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THE UNIVERSITY OF TEXAS, SCHOOL OF MEDICINE
GALVESTON

THE DISTRIBUTION OF CARBON DIOXIDE BETWEEN COTTONSEED OIL AND A SOLUTION OF SODIUM BICARBONATE*

BYRON M. HENDRIX AND BERNARD BERNARDONI

Jacobs (1) has shown that carbonic acid enters living cells more rapidly than any other acid. He states that it diffuses so promptly into starfish eggs which have been stained with neutral red, that it is not possible to follow the change of color by means of the microscope. The shift in pH of the protoplasm of living cells caused by the penetration of carbon dioxide may not bear any obvious relation to the pH of the surrounding medium. Jacobs (2) has shown that the flowers of *Symphytium Peregrinum* develop intracellular acidity when immersed in M/2 sodium bicarbonate solution of pH 7.4 just as rapidly as when placed in a solution of carbon dioxide in distilled water of pH 3.8. He has also shown that if an indicator solution is separated from a solution of sodium bicarbonate and carbon dioxide by a layer of xylene or cottonseed oil, the indicator becomes markedly acidic as shown by the distinct change in color, even though the sodium bicarbonate solution had a pH greater than 7. These results led Jacobs to conclude that carbon dioxide is very readily soluble in the lipoids of the cell membrane and easily passes through the membrane into the protoplasm of the cell.

In view of these observations and suggestions of Jacobs, we became interested in determining to what extent carbon dioxide would pass from a bicarbonate solution which contained varying amounts of free carbon dioxide to a neutral oil such as cottonseed oil when the oil and bicarbonate were brought into contact with each other in such a way that there could

*This paper has been abstracted from a thesis presented by Mr. Bernardoni to the Graduate School of The University of Texas in partial fulfillment of the requirements for the degree of Master of Arts.

A preliminary report of this paper was presented at the twenty-sixth (Philadelphia) meeting of American Society of Biological Chemists, April, 1932. For abstract of this report see *Journal of Biological Chemistry*, Volume 97, page xcv, 1932. Received for publication April 3, 1944.

be no loss of carbon dioxide from the system. While cottonseed oil is distinctly different from the lipoids of cell membranes and of nervous tissue, it seems probable that it would have a not very different solvent action upon carbon dioxide. We have compared the solvent effect of cottonseed oil upon carbon dioxide with that of olive oil and have found essentially no difference between these oils in this respect. It is a safe assumption that any neutral fatty oil would have served our purpose equally well.

Methods

Reaction Vessels. Oil sampling bottles which were kindly loaned us by the Galveston Laboratories were used as "reaction" vessels. These bottles could be closed by means of a cork and sealed with paraffin in such a way that no carbon dioxide escaped during the course of the experiment. Several tests were made in order to determine the impermeability of this form of closing the vessel, for example, a 0.05 M solution of sodium bicarbonate which contained free carbon dioxide with pH of 7.20 was placed in a series of bottles on February 1, and kept at 37.5° C. On February 8, one of the bottles was opened and the pH found to be 7.16; the same pH was found for the solution in a second bottle which was opened February 10.

Oil. An abundant supply of cottonseed oil was kindly furnished us by the Galveston Laboratories. The refined oil was treated with slightly more sodium hydroxide solution than was required to neutralize the residual acidity. The oil and alkali solution were thoroughly mixed by shaking them together for about thirty minutes. The oil was then allowed to separate and was decanted from the aqueous layer, and was finally filtered twice through a good grade of filter paper. The oil was then found to have an acidity equivalent to 0.005% sulphuric acid or 0.0032% carbonic acid when titrated in the presence of alcohol, using phenolphthalein as the indicator.

The pH Determinations. These determinations were made by means of the quinhydrone electrode and the saturated calomel electrode. The E.M.F. was read by means of the

Leads and Northrup hydrogen ion potentiometer, and lamp and scale galvanometer. Tenth normal hydrochloric acid, which was assumed to have a pH of 1.08, was used as a standard for the pH determinations. All pH determinations were made at room temperature. The problem of making the pH determinations in such a way that there would be no loss of carbon dioxide, was given considerable attention. We did a control series of determinations by filling a number of our reaction bottles with 0.05 M sodium bicarbonate—carbon dioxide solutions of determined pH and again determining the pH by opening the bottles, adding the quinhydrone, inserting the platinum electrode and reading the E.M.F. in the usual way. While there were slight variations in the second pH determinations, these variations were not toward a higher pH which would have occurred if there had been any considerable loss of carbon dioxide in the time required to make the reading.

Carbon Dioxide Determination. When carbon dioxide determinations were made, the manometric method described by Van Slyke and Neill was used. The carbon dioxide which was dissolved in oil was determined in the following manner: a weighed amount of oil was placed in a flask with a weighed amount of sodium hydroxide solution which contained only a small but known amount of carbon dioxide. The oil and solution were shaken together and allowed to stand until the oil and solution separated in definite layers. The carbon dioxide was then determined in a aliquot portion of the sodium hydroxide solution. Since a large excess of sodium hydroxide was used, the carbon dioxide was completely extracted from the oil.

The Sodium Bicarbonate—Carbonic Acid. The solution used was 0.05 M with respect to sodium bicarbonate. Before passing carbon dioxide into it, the pH was about 8.1. The amount of carbon dioxide added varied with the pH desired for a particular series. In making these solutions the pH was roughly determined by means of a suitable indicator, but the quinhydrone electrode was always used in determining the pH of the control in each series.

Discussion of Results

At the beginning of this work, it seemed necessary to roughly determine the solubility of carbon dioxide in the cottonseed oil. Carbon dioxide was bubbled through some of the oil for thirty minutes, when it was assumed that the oil was saturated with carbon dioxide at approximately atmospheric pressure. Samples of this oil were treated with neutral alcohol and titrated with 0.1 N sodium hydroxide using phenolphthalein as the indicator. The results of our solubility determinations will not be given here as we are very much in doubt about their accuracy. They did show, however, that carbon dioxide is readily soluble in oil.

Figure 1 gives the results of the first experiment in which we determined the pH of the aqueous phase by the method

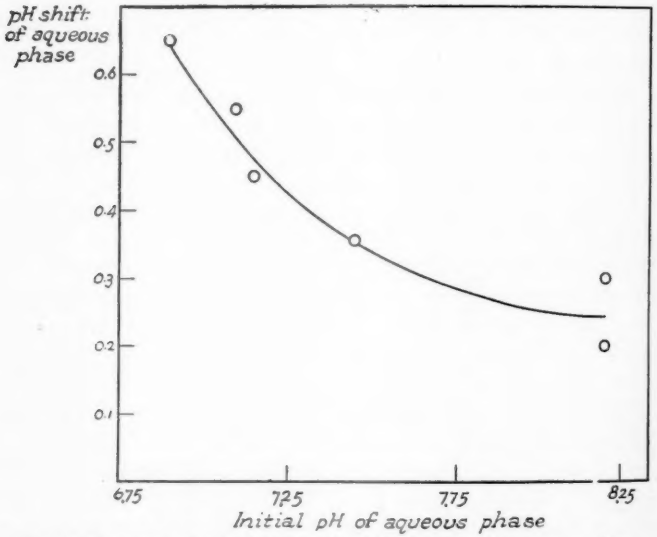

Fig. 1. The effect of initial pH on the shift in pH of the aqueous phase.

which we finally adopted. The control tubes (those completely filled with sodium bicarbonate and carbon dioxide dissolved in water) showed a change from pH 7.08 at the beginning of the experiment to pH 7.10 and 7.13 after stand-

ing four days at 37.5° C. while the aqueous phase of the tubes which contained half oil and half solution, changed in four days to about pH 7.60. In four of the five tubes, the pH determination checked each other within 0.08 of a pH unit. It seems most likely that there must have been some loss of carbon dioxide from tube No. 6. In this experiment, the pH of the aqueous phase changed from 7.16 to about 7.60. This experiment was originally designed to ascertain whether there is any essential difference between cottonseed oil and olive oil for the purposes of these experiments. An inspection of the data in Table I shows that the shift in pH did not vary with the different oils.

TABLE I

pH Shift of a $NaHCO_3$—H_2CO_3 Solution When Exposed to Neutral Olive and Cottonseed Oils

Temperature 37.5° C.

Tube No.	Contents	pH of Aqueous Phase		
		First Day	Eighth Day	Tenth Day
3	$NaHCO_3$—H_2CO_3 solution (control)	7.20		
4	$NaHCO_3$—H_2CO_3 solution (control)		7.16	
5	½ volume olive oil ½ volume solution		7.57	
6	½ volume olive oil ½ volume solution		7.59	
7	½ volume cottonseed oil ½ volume solution		7.62	
8	½ volume cottonseed oil ½ volume solution		7.59	
9	½ volume cottonseed oil ½ volume solution		7.64	
10	$NaHCO_3$—H_2CO_3 solution (control)			7.16
11	½ volume olive oil ½ volume solution			7.59
12	½ volume olive oil ½ volume solution			7.62
13	½ volume cottonseed oil ½ volume solution			7.61
14	½ volume cottonseed oil ½ volume solution			7.64
15	½ volume cottonseed oil ½ volume solution			7.62

The shift in pH varied with the initial pH of the aqueous phase. The most acid solution with a pH 6.96 (see Table I) shifted 0.58 of a pH unit while the most alkaline solution with a pH 8.19 shifted only 0.21. In Figure 1, we have plotted the pH shift against the initial pH in those experiments in which we felt reasonably sure that equilibrium had been reached. If this curve were extended in the direction of a higher pH, it would indicate that cottonseed oil would take up some carbon dioxide from a solution of sodium bicarbonate and sodium carbonate which has a pH at least as high as 9.

The rate of shift in the pH of the aqueous phase of the sodium bicarbonate—carbonic acid solution—oil system is shown by experiments reported graphically in Figure 2. The curve indicates that equilibrium has been reached (or nearly so) in forty-eight hours. It can be shown that about 36% of the carbon dioxide which finally becomes dissolved in the oil, leaves the solution within the first two hours of the experiment, and only about 26% of the carbon dioxide passes into the oil during the second twenty-four hours.

In order to show that the carbon dioxide really dissolved in the oil, we decided to determine the amount of carbon dioxide in both the oil and aqueous phases of the system, and to compare the amount of carbon dioxide lost by the solution with the amount gained by the oil. Four such series of experiments were performed but only one is reported here. (See Table II and Figure 3.) The actual loss of carbon dioxide from the aqueous phase checks fairly well with the actual gain by the oil. The determinations of total carbon dioxide in the aqueous phase are undoubtedly more accurate than the determinations of carbon dioxide in the oil phase. There was always some possibility of gain or loss of carbon dioxide when it was extracted from the oil by sodium hydroxide solution. There was always a danger of gain of carbon dioxide from the air by the sodium hydroxide solution and also a chance of loss to the air when the oil was being transferred from the "reaction" vessel to the sodium hydroxide solution. These two errors tended to neutralize each other, but we are

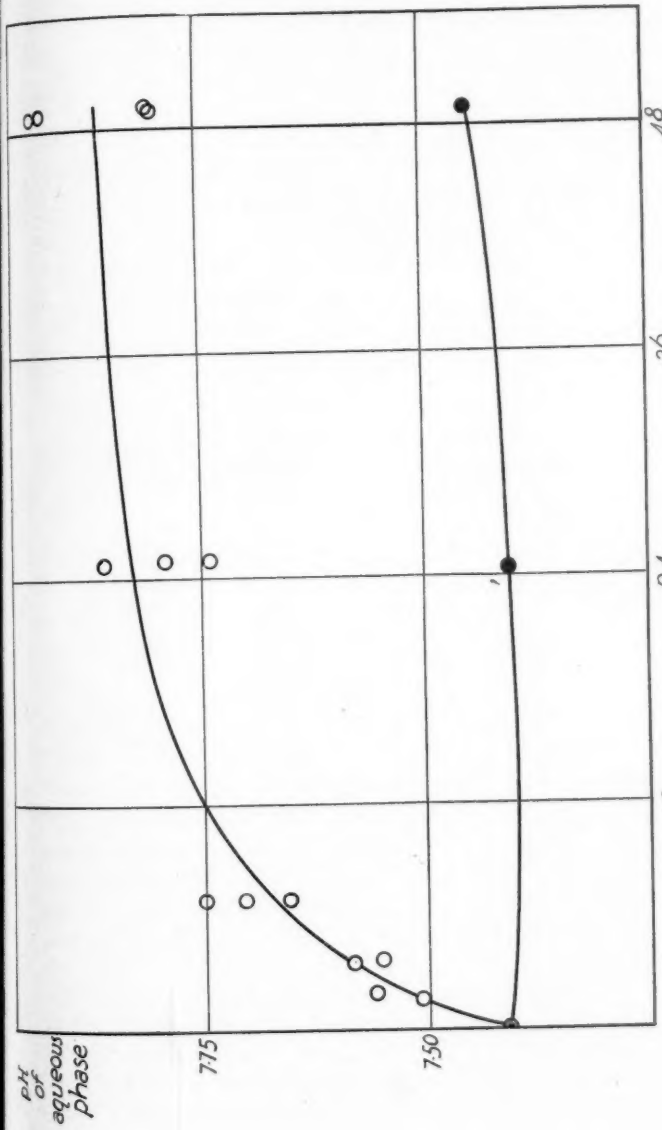

Fig. 2. The rate of change in pH of the aqueous phase of the system, oil-carbon dioxide-bicarbonate solution: closed circles are controls, open circles solution in contact with oil.

TABLE II

The Loss of Carbon Dioxide from the Sodium Bicarbonate-Carbonic Acid Solution and the Gain in the Amount of Carbon Dioxide Dissolved by the Neutral Oil

Date	Tube No.	Contents	pH of Solution	Volume CO_2 Lost by Solution cc.	Volume CO_2 Gained by Oil cc.
1st day	1	$NaHCO_3$—H_2CO_3 solution (control)	6.96		
2d day	3	$NaHCO_3$—H_2CO_3 solution (control)	6.96		
2d day	4	63.2 gms. solution 50.4 gms. oil	7.25	4.38	4.16
2d day	5	64.2 gms. solution 49.2 gms. oil		4.20	4.74
3d day	6	$NaHCO_3$—H_2CO_3 solution (control)	6.95		
3d day	7	67.7 gms. solution 48.0 gms. oil	7.44	6.30	5.11
3d day	8	63.9 gms. solution 44.6 gms. oil		5.59	5.89
4th day	9	$NaHCO_3$—H_2CO_3 solution (control)	6.98		
4th day	10	62.1 gms. solution 47.2 gms. oil	7.44	5.89	6.25
4th day	11	58.1 gms. solution 52.4 gms. oil		6.60	6.64
8th day	12	62.7 gms. solution 49.8 gms. oil	7.56	6.60	6.81
8th day	14	64.6 gms. solution 48.9 gms. oil	7.64	6.61	7.25

not at all certain that they did so with any degree of exactness. In a few cases, the amount of carbon dioxide in the oil was so large that we are convinced the extracting alkali was seriously contaminated by carbon dioxide from the air. These results do show, however, that the carbon dioxide is actually dissolved in the oil.

In calculating the loss of carbon dioxide from the aqueous phase, we have taken the average carbon dioxide content of four control tubes as the actual per cent of carbon dioxide in the aqueous phase at the beginning of the experiment. The total carbon dioxide found in the oil when the deter-

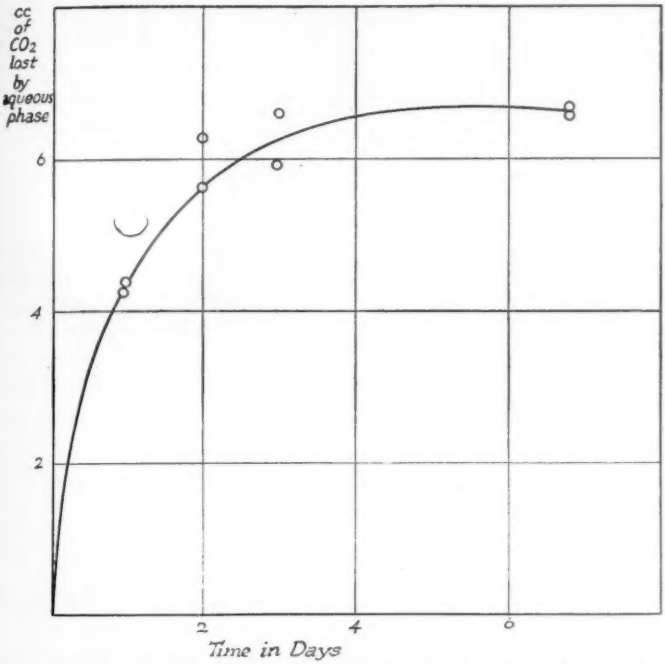

Fig. 3. The rate of loss of carbon dioxide from the aqueous phase of the oil-carbon dioxide-bicarbonate solution system.

minations were made, was corrected by blank determinations on the oil and on the sodium hydroxide which was used to extract the carbon dioxide from the oil.

We have attempted to calculate the distribution coefficients from our data, but have become very doubtful about the significance of such calculations. As mentioned above, some carbon dioxide passes from a 0.05 M sodium bicarbonate solution even when no "free" gas is present, but we are not justified in considering the total carbon dioxide as diffusible into the oil phase. The distribution of the carbon dioxide obviously depends upon several factors, namely, the solubility in water, solubility in oil, amount of base in solution and the total carbon dioxide present. In these aqueous solutions, the carbon dioxide was present in the following forms: sodium

bicarbonate, bicarbonate ions, carbonic acid and anhydrous carbon dioxide. We have no knowledge of the form in which carbon dioxide exists in solution in the oil, but it is quite certain that sodium bicarbonate does not dissolve in it. In view of these considerations, it seems impossible to calculate from our results, distribution coefficients which would show the relative solubility of carbon dioxide in oil and water.

Summary

Aqueous solutions of bicarbonate and carbon dioxide in equilibrium with cottonseed oil become more alkaline.

The shift in pH is greatest in the solutions containing most free carbon dioxide.

Bicarbonate solutions which contain no added carbon dioxide become more alkaline when brought in contact with cottonseed oil.

The loss in carbon dioxide by the aqueous phase is nearly the same as the carbon dioxide dissolved by the oil.

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AN OUTBREAK OF FOOD POISONING RESULTING FROM EATING CONTAMINATED RAW OYSTERS

ROBERT WISE, JOE B. WINSTON, AND CARL A. NAU*

An outbreak of food poisoning involving 28 out of a possible 65 members of a medical group occurred in Galveston, Texas, as the result of eating raw oysters at a banquet given on the night of February 26, 1944. These 28 individuals were all confined to their beds for half a day or longer; appeared to be quite ill; but all made a complete and rapid recovery.

CLINICAL COURSE

The clinical manifestations of all cases were very similar. The earliest symptom noted was usually intense nausea. This was followed by profuse and violent vomiting—somewhat of a projectile type. In a few instances vomiting occurred "without warning." Diarrhea was of an explosive type with 1 to 15 watery stools. There was no blood reported seen in any stool. A few students complained of "gas." Three-fourths of those sick reported having fever up to 101° F. The attacks had an onset varying from 27 to 46 hours after the dinner on Saturday night (February 26) and lasted 6 to 24 hours. Most of the men felt weak and exhausted when they returned to their work.

It is interesting that all involved who are self-admitted relatively "heavy drinkers" and who ate oyster cocktail, *did not* manifest the symptoms described. Conversely, all of those who ate oyster cocktail but drank no alcoholic drinks whatever, got sick.

SCOPE OF STUDY

One of us (C.A.N.) was called on Monday night (February 28) and found most of the 26 in bed.

This finding provoked a study which consisted of:

1. Obtaining clinical histories of the 26 cases.

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2. A determination of the foods eaten at various meals; source of these foods and methods of preparation and handling.
3. Bacteriological examination of oysters obtained from the same market and beds as those thought to be responsible for the outbreak.
4. Inspection of the oyster shucking sheds and wholesale market—together with methods of handling the oysters.
5. Bacteriological examination of water overlying the oyster beds.
6. Determination of the chloride content of the water overlying the beds.

Course of Events

From conversations with various members of the group it was learned that some members do not eat with the group except on "rare" occasions, this banquet being one of those "rare" occasions. Some of these men were among those who became ill. They had eaten only the one meal at the house. Also, some of the men who ate at the house regularly had missed the Saturday noon meal and also, did not eat any meal on Sunday at the house. Thus, it was evident that all those who became ill had eaten the Saturday night banquet-meal at the house; and only those who ate this meal became sick. This meal was, therefore, thoroughly analyzed epidemiologically.

It consisted of: Raw oyster cocktail (3–4 oysters per cocktail); fresh avacado salad with freshly made (home-made) mayonnaise or French dressing; fresh fried chicken; mashed potatoes; cream gravy; canned English peas; canned yellow corn; canned cranberry sauce; olives, celery, pickles; canned crushed pineapple; hot rolls; coffee and cream; ice cream; plain vanilla cookie; cheese crackers; sweet wine.

The raw oysters were purchased from the local market, being obtained in one-gallon containers. Four gallons were purchased and were delivered early on Friday morning, February 25. On this same day, two gallons were fried and served at noon. There were no known complaints.

The local oyster markets are not "certified." They obtain their oysters from local beds whenever possible; and shucking is carried on under some questionable sanitary practices.

The remaining two gallons of oysters left over after Friday noon were put into the freezing compartment immediately upon delivery and were kept frozen until late Saturday afternoon, February 26, at which time they were "thawed out" and served as raw cocktails to those present at the banquet. Some men reported eating none of the oysters; others ate one-half, one or two oysters. And several ate more than one cocktail (four oysters). In general, the cocktails were enjoyed by all who were "trained to eat raw oysters."

The avacados were purchased on the local market and were served raw with a freshly prepared dressing made in the kitchen of the house. The chicken was purchased in Houston and was delivered dressed and drawn and well-iced on Saturday morning, February 26. It was kept in ice until fried Saturday afternoon. The potatoes were freshly cooked and served mashed and hot. The ice cream and cream were obtained from a widely marketed pasteurized local supply.

No outbreak of food-poisoning was reported in Galveston concurrently with that in the house. The meals were all planned by a student-manager who also makes all purchases. The preparation of food was done by Negro helpers.

No one complained of feeling sick until early Monday morning, February 28, when nausea was noted by a number of students. Between 5:00 A.M. and 8:00 P.M. on this day, 26 men "took to their beds." The remaining ones were kept busy "cleaning up" and doing "emergency nursing."

The following table gives the percentage of the attacked and unattacked who ate the different foods served at the banquet:

Foods served:	Percentage of Personnel Eating Different Foods	
	Attacked	Not Attacked
Oysters	100	55
Chicken	100	100
Salad	97	85
Potatoes	97	90
Cream gravy	80	80
Peas	100	95
Corn	100	80
Rolls	100	100
Coffee	80	80
Cranberries	72	80
Olives	80	80
Celery	72	80
Pickles	80	75
Pineapple	86	75
Ice cream	100	90
Cookie	80	80
Cheese crackers	61	70
Wine	80	80

According to data obtained from the sick students, the interval of time elapsing between the eating of the implicated food and the earliest symptom, are as follows:

27 hours	2	38 hours	2
29 hours	1	41 hours	1
32 hours	1	42 hours	1
33 hours	1	44 hours	2
34 hours	1	45 hours	1
35 hours	8	46 hours	1
36 hours	4	Total	26

Laboratory Findings

A. Bacteriological Findings on Oysters.

All of the oysters delivered to the house were consumed before the onset of the first symptom. None remained for bacteriological study. The seller, however, kindly and generously furnished additional oysters obtained by him from the same source and from the same oyster beds.

Bacteriological Examination of Oysters

Two hundred milliliters of oysters were mixed with 200 ml. of sterile physiological saline in a sterile quart jar and disintegrated by shaking. The liquor was inoculated into five series of lactose broth in 10, 1, 0.1, and 0.001 ml. amounts.

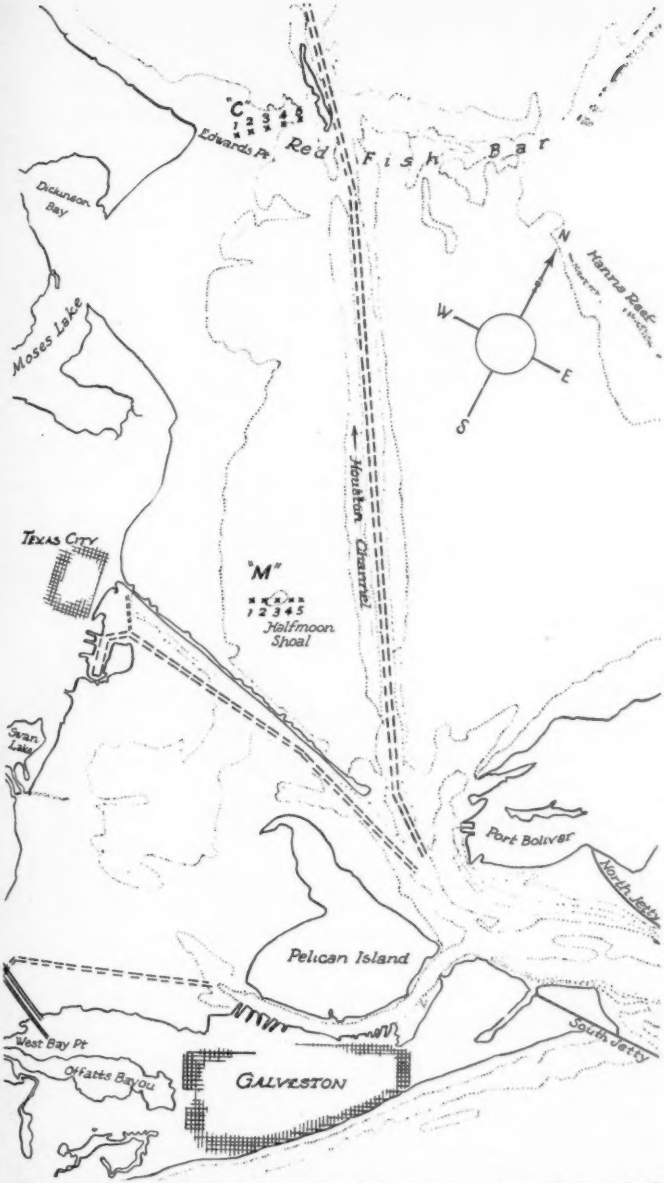

Fig. 1. Map showing area from which oysters eaten and examined bacteriologically were obtained and specific locations (X) from which water samples were collected.

Confirmatory and completed tests for coliform bacteria were made by streaking tubes showing gas formation to plates of eosin methylene blue agar and transferring typical colonies to lactose broth. The results were recorded as the most probable number of coliform organisms per 100 ml. of oysters.

	MPN
Sample C	184,000
Sample M	7,000

For the isolation of pathogenic bacteria of the enteric group 10 ml. of liquor were inoculated into tetrathionate broth and streaked after 48 hours incubation to SS agar. No pathogens were isolated.

B. Bacteriological Findings on Water Overlying Suspected Beds.

Five samples of water were collected March 23, 1944, over each oyster bed and examined for evidence of fecal pollution according to "Standard Methods of Water Analysis, current edition, American Public Health Association." The results were recorded as the most probable number of coliform bacteria per 100 ml. of water.

Source	Water Sample	Most Probable Number of Coliform Organisms Per 100 ml.
Oyster Bed C	1	350
	2	1,600
	3	920
	4	broken
	5	920
Oyster Bed M	1	350
	2	1,600
	3	350
	4	540
	5	1,600

C. Chloride Determinations.

Source	Water Sample	Chloride p.p.m.
Oyster Bed C	1	2,200.0
	2	2,080.0
	3	2,000.0
	4	broken
	5	1,400.0
Oyster Bed M	1	2,740.0
	2	2,520.0
	3	2,440.0
	4	2,840.0
	5	2,520.0

Determinations for chloride were made according to the "Standard Methods of Water Analysis published by the American Public Health Association."

The chloride content of the Gulf water is approximately 14,700 P.P.M.

An inspection was made of the facilities of the shucking shed and of the methods of shucking and handling of the oysters. Many practices required for certification were not being carried out; and there appeared to be much opportunity for contamination of the shucked raw oyster.

Conclusions

1. Based upon epidemiological evidence, it may be concluded that raw contaminated oysters were the cause of the outbreak.

2. Oysters obtained from the same beds and through the same market as those responsible for the outbreak showed a high content of coliform organisms indicating fecal contamination.

3. Water obtained from over the beds from which the involved oysters were obtained, show a high content of coliform organisms, indicating fecal contamination.

4. Chloride determinations of the water overlying the beds, when compared to the chloride content of Gulf water on the same day, indicate considerable dilution by fresh water. This dilution can be accounted for by an abnormally large discharge of fresh water from the streams whose water shed had received an excessive amount of rainfall just prior to the day of sampling.

5. The oysters responsible for the outbreak may have been contaminated while on the beds and/or in the process of harvesting and/or preparation for eating.

6. None of the men who were "self admitted heavy drinkers" at the banquet and who ate oyster cocktail became sick. Whereas, all of the men who did not drink alcoholic beverages and who ate oyster cocktail became sick.

Further studies on oyster contamination in the Galveston area is contemplated.

The authors wish to acknowledge the generous assistance and coöperation of the owner of the oyster market, Mr. Jack Tanner of the Texas Game, Fish and Oyster Commission, and all of the men who participated in the banquet. Without such help this study could not have been made.

THE RELATION OF THE EXCRETION OF GASTRIC JUICE AND OF URINE TO THE ALKALOSIS OF HYDRAZINE INTOXICATION IN THE RABBIT

BYRON M. HENDRIX, D. BAILEY CALVIN, AND MAX M. GREENBERG*

Hydrazine has been regarded as a specific liver poison, and, for this reason, has been used frequently in metabolic studies in order to obtain information about certain liver functions. In 1924, Hendrix and McAmis showed that alkalosis develops when hydrazine sulphate is given to dogs in suitable subcutaneous doses. Evidence presented then indicated that alkalosis is associated with a decrease of chloride in the blood. Dogs which have been given hydrazine vomit excessively so that the alkalosis does not appear to be caused by a deranged liver function, but by a loss of hydrochloric acid from the stomach, which, in turn, depletes the store of chloride in the blood and other body fluids. However, there are some features of this alkalosis which are obscured by excessive vomiting. This may modify the alkalosis to a considerable extent because anhydremia usually brings about a decrease in the CO_2 capacity of the blood. Such conditions may mask, in part, the hydrazine effect. Vomiting makes it difficult to obtain urine samples which have not been contaminated. Underhill and Baumann reported a more alkaline urine after hydrazine injections into dogs while we have not been able to obtain such results. This was due largely to contamination of the urine with vomitus, and it is seldom possible to obtain complete samples of urine by catheterization without infecting the bladder with urea splitting organisms.

In order to determine, if possible, the relation of this alkalosis to the loss of chloride through the stomach and the character of the urine after hydrazine injections, we have studied the effect of this drug upon rabbits, which do not vomit, so

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that chloride cannot be lost from the body by this means. Since there is an increase in CO_2 capacity of the blood of the rabbit after hydrazine intoxication, certain ways are open to us for the study of alkalosis.

Experimental

Mature rabbits were used in all of the experiments. The stock colony was kept on a grain-alfalfa diet. Animals were fasted for 24 or 48 hours, with urine collection, prior to the first blood sampling. This constituted the initial control period. All animals were fasted a further 48- or 72-hour period (72-120 hours total fast), a second blood sample was taken, and were sacrificed at the end of this time. Hydrazine sulphate injected animals were given 40 mg. per kg. of the salt (dissolved in 10–15 ml. of water with the aid of heat), subcutaneously, shortly after the first blood sample was obtained.

All blood specimens were removed by heart stab, about 20 ml. being the usual amount taken for analysis. Potassium oxalate was used as anti-coagulant. A portion of the blood was allowed to clot to obtain serum for base determination. The animals were stunned at the end of the final period, the stomach was quickly removed, opened, and thoroughly washed, and the washings and contents were diluted to 600 cc. and filtered. The clear filtrate was used for gastric analyses.

Urine was collected under toluene, care being exercised to have bottles and cages thoroughly cleaned and changed often to prevent bacterial putrefaction. The bladder was emptied by abdominal massage at the end of each period. Urine specimens for each period were pooled for analysis.

The following determinations were made on blood and urine specimens for each period: whole blood, plasma, and gastric chlorides (Van Slyke and Sendroy); serum and urine total base (Keys); plasma carbon dioxide capacity (Van Slyke and Neill); hemoglobin (Cohen and Smith); red cell volume, using Mayo 6 ml. tubes at about 3,000 rpm. for 30 minutes; urine ammonia (Van Slyke and Cullen); urine chlorides, Volhard-Arnold; urine acidity (Folin); phosphates by the uranium acetate titration method using cochineal as indicator (Malot); total and inorganic sulphates (Rosenheim and Drum-

mond); organic acids by the Greenwald modification of the Van Slyke and Palmer technique, and pH by the colorimetric method (Clark).

In order to arrive at an interpretation of our data, we have found it necessary to use averages of data on the groups of animals studied. Thus, averages have been obtained for: (a) the preliminary period, (b) the period after hydrazine, and (c) the period of fast in controls corresponding roughly in length to the hydrazine periods. Unless otherwise indicated, comparisons have been made between the data from the two latter periods (b and c).

Results

Tables I and II contain the analytical data which were obtained from these experiments. The first series (Table I) includes 15 experiments on 10 different animals. Systematic urine analysis was not attempted in this series and the CO_2 capacity was determined upon whole blood. In the second series (Table II), there were 14 experiments on 14 animals and 6 control experiments on 6 animals. Averages of the CO_2 capacity on the first series (Table I) were 45.7 volumes per

TABLE I*

Animal No.	Date†	CO_2 Capacity of Blood Before Hydrazine	CO_2 Capacity of Blood After Hydrazine	Time Between Blood Samples
	1934	Vols. Per Cent	Vols. Per Cent	Hours
I	May 4	41.4	46.7	48
I	May 14	44.2	56.3	48
II	May 5	40.0	67.8	54
II	May 14	52.5	66.5	24
III	May 8	46.8	56.5	24
III	June 9	44.7	48.3	24
IV	May 18	52.7	55.5	48
V	May 21	47.2	68.7	24
V	June 12	45.0	52.6	48
V	June 21	42.2	51.3	48
VII	June 5	34.7	43.5	24
VIII	May 24	44.0	63.5	48
IX	June 8	42.3	43.8	24
XI	June 13	53.0	58.8	48
XII	June 20	54.2	55.7	48

*The data in this table have been taken from a thesis presented by Mr. Max M. Greenberg, in July, 1934, to the Faculty of the Graduate School of The University of Texas in partial fulfillment of the requirements for the degree of Master of Arts.
†The date of the beginning of each experiment is given.

cent CO_2 before hydrazine and 55.7 volumes per cent after. In the second series (Table II) the average CO_2 capacity before hydrazine was 43.08 volumes per cent and after hydrazine was 56.33 volumes per cent. This increase in CO_2 capacity is so definite that there is no doubt that alkalosis is produced by hydrazine administration.

Careful attention has been given to changes in blood and urine which may show the cause of the alkalosis. Hendrix and McAmis have suggested that the shift in the ratio of sodium to chloride in the blood may indicate the cause of the alkalosis which results from hydrazine intoxication in dogs. No determinations which would enable us to calculate such a ratio were made in the first series of experiments, but in the second series, we have data from which the total base to chloride ratios have been calculated. That these ratios increased after hydrazine is shown by an average ratio of 1.60 after hydrazine, while before the injections, the ratios averaged 1.50, and in the control animals, which had fasted as long as the hydrazine animals, the ratio was 1.52. This shows distinctly that the chloride had decreased with respect to the total base of the plasma but does not, of necessity, show an absolute decrease in the chloride ions. As a matter of fact, reference to Table II shows only an insignificant change of chloride in the plasma after injections, the average amount being 98.9 ml. 0.1N chloride per 100 ml. To be sure, the average before injection was found to be 102.2 ml. 0.1N but in the control animals, the amount averaged 99.8 ml. 0.1N chloride per 100 ml. These differences are probably not significant.

The total base of the serum varied somewhat more than the chloride, averaging 158.2 ml. 0.1N base per 100 ml. after hydrazine injections, while before injection it averaged 155.2 ml. 0.1N. The controls averaged 151.03. The comparisons between the injected animals and the controls are to be preferred. This shows an increase of 7.2 ml. of total base per 100 ml. of serum. Significance can be attached to this increase in serum base only if some loss of anions can be accounted for either by excretion or migration to other parts

TABLE II

Animal No.	Wt. kg.	Plasma CO_2 Vols. per cent.	Plasma Chloride per 100 ml. ml. 0.1N	Serum Base per 100 ml. ml. 0.1N	Base to Chloride Ratio	Urine Volume ml.	Urine Base ml. 0.1N	Urine Total Acidity ml. 0.1N	Urine Phosphate ml. 0.1M	Urine Organic Acid ml. 0.1N	Urine pH	Free Acid in Gastric Content ml. 0.1N	Chloride in Gastric Content ml. 0.1N	Remarks
6	2.6	39.1	98.7	161.8	1.64	215.	92.2	25.6	24.7	27.5	6.2	.....	.....	24 hr. fasting period.
6	....	61.1	90.4	155.5	1.72	160.	179.5	118.9	83.8	57.6	4.6	85.2	128.0	3 days after hydrazine injection.
11	2.5	57.0	102.2	149.0	1.46	105.	58.0	19.8	17.3	14.7	5.8	.....	.....	48 hr. fast, 24 hr. urine.
11	....	53.5	106.3	156.8	1.47	180.	171.3	84.8	47.8	55.7	4.8	101.4	103.5	3 days after hydrazine.
12	3.5	48.1	91.0	138.0	1.51	105.	98.1	50.4	32.5	27.5	4.6	.....	.....	24 hr. fasting period.
12	....	64.5	84.7	146.6	1.73	90.	123.7	62.9	32.0	53.1	4.8	230.0	279.0	2 days after 1st, 1 day after 2d hydrazine injection.
13	3.0	35.5	105.2	154.7	1.40	125.	195.2	124.9	102.7	158.2	5.8	.....	.....	48 hr. fasting period.
13	....	54.2	97.6	149.5	1.53	185.	225.6	186.6	133.2	71.0	4.6	146.4	202.0	3 days after 1st, 2 days after 2d hydrazine injection.
14	2.5	45.6	106.6	156.0	1.45	140.	283.2	162.2	122.7	57.6	4.8	.....	.....	60 hr. fasting period.
14	....	64.7	107.8	161.5	1.50	260.	255.0	163.2	118.4	86.4	4.4	106.7	159.0	3 days after 1st, 2 days after 2d hydrazine injection.
15	2.5	45.2	100.2	160.0	1.59	400.	222.3	56.8	60.1	42.8	6.2	.....	.....	48 hr. fasting period.
15	....	63.1	100.8	163.0	1.63	175.	129.6	69.7	50.5	26.7	4.6	68.5	96.7	3 days after 1st, 2 days after 2d hydrazine injection.
16	2.4	42.5	103.8	155.5	1.50	130.	184.0	60.9	56.2	31.4	6.3	.....	.....	48 hr. fasting period.
16	....	59.9	89.9	157.3	1.71	205.	244.4	97.9	73.4	60.8	4.6	81.6	94.3	3 days after 1st, 2 days after 2d hydrazine injection.
17	2.5	51.3	103.2	166.3	1.57	225.	174.2	54.5	46.3	40.4	5.8	.....	.....	48 hr. fasting period.
17	....	68.7	98.1	156.0	1.59	420.	217.2	138.0	100.2	66.4	4.4	71.2	91.4	3 days after 1st, 1 day after 2d hydrazine injection.
18	2.0	52.2	102.3	154.0	1.50	240.	271.8	12.8	37.8	42.3	7.6	.....	.....	48 hr. fasting period.
18	....	80.6	97.7	158.0	1.63	250.	230.1	145.4	120.3	66.5	4.5	77.8	103.6	3 days after 1st, 2 days after 2d hydrazine injection.
19	2.2	37.2	105.2	153.0	1.45	225.	217.0	46.7	56.5	36.7	6.3	.....	.....	48 hr. fasting period.
19	....	37.8	105.7	156.3	1.47	225.	135.6	66.1	56.9	30.7	5.8	42.7	83.2	72 hrs. cont'd fast. Control.
20	2.3	24.2	109.0	166.3	1.53	90.	153.2	21.1	18.2	19.7	6.3	.....	.....	48 hr. fasting period.
20	....	39.5	91.0	152.0	1.67	175.	152.8	101.2	73.8	45.4	4.9	19.0	156.0	72 hrs. cont'd fast. Control.
21	3.0	41.1	90.0	139.0	1.54	200.	207.6	51.8	62.9	44.2	5.6	.....	.....	48 hr. fasting period.
21	....	51.9	97.8	138.5	1.42	530. (?)	253.5	65.1	106.8	47.5	6.2	99.8	125.3	72 hrs. cont'd fast. Control.
22	2.3	36.5	94.4	155.0	1.64	325.	255.7	56.8	54.1	48.0	6.4	.....	.....	48 hr. fasting period.
22	....	44.4	90.0	151.0	1.67	250.	230.6	120.0	98.6	48.0	5.3	71.8	93.9	72 hrs. cont'd fast. Control.

of the body. Our data give no evidence of extra loss of anions through the urine.

In spite of the fact that rabbits do not vomit, it occurred to us there might be a considerable increase in the amount of free acid secreted into the stomach of the rabbit after hydrazine intoxication. We have killed most of our animals in the second series immediately after taking the last sample of blood and determined the amount of free acid in the gastric contents. An average free acid equivalent to 39.9 ml. 0.1N HCl per kilogram of body weight was found in the stomach content of the hydrazine animals, while controls which had fasted just as long had an average equivalent to 24.0 ml. 0.1N HCl per kilo., or an increase of 15.9 ml. of 0.1N acid for the hydrazine animals. The average difference in CO_2 capacity between the hydrazine treated and the control animals was 17.6 volumes per cent, which is equivalent to 0.76 millimol or 7.6 ml. of 0.1N base. This shows about 4 times as much acid in the stomach as was lost potentially from the plasma, if we assume that there are 50 ml. of plasma per kilo of body weight.

Although there was an increase both relatively and absolutely in gastric free acidity following hydrazine, this was not accompanied by a significant fall in plasma chloride values. The probable sources, therefore, for the extra chloride of the gastric juice are extracellular fluid and the erythrocytes. We have obtained some evidence that the chloride content of the erythrocyte decreases after hydrazine injections. On the basis of cells per 100 ml. of whole blood, the respective values were 17.7 ml. for control, and 15.2 ml. after hydrazine, of 0.1N chloride. This shows a loss from the erythrocytes of 2.5 ml. of 0.1N chloride per 100 ml. of blood. Taking the average rabbit weight at 2.5 kg. and the estimated blood volume equal to 8 per cent, this would indicate a total loss from the blood of about 5 ml. of 0.1N chloride, representing only about one-third of the extra acid found in the stomach. It seems most likely that changes in extracellular fluid may account for the additional chloride found in the stomach.

The suggestion presented itself that the excretion of increased amounts of acid in the urine might account for the

retention of an increased amount of available base in the blood. Data in Table II show that an average of 29.9 ml. of 0.1N acid (titratable acidity) were excreted per day by the hydrazine treated animal and 29.8 ml. of 0.1N per day before the treatment. Control animals which had fasted as long as the hydrazine animals excreted 36.6 ml. per day. This shows, of course, that the excretion of acid was not a factor in the development of alkalosis. It is interesting to note, however, that the pH of the urines was lower after hydrazine than in the case of the control fasting animals. The median pH of the urines of the experimental group was 4.65 while in the fasted control animals it was 5.35. The urine volumes of the hydrazine animals were quite low, so that the acid excreted per ml. of urine was higher than in the controls, which explains the lowered observed pH.

The increase in CO_2 capacity of the plasma would be expected to bring about greater excretion of cations in the urine. This has been observed in the alkaline tide in man and other animals as well as in certain other conditions in which the available base of the blood had increased or the pH of the plasma had shifted even slightly to the alkaline side. The hydrazine animals, however, showed almost exactly the same amount of base excretion per day as the controls which had fasted an equal length of time.

The results of this study of alkalosis do not give any evidence of change of liver function in relation to the acid-base equilibrium under conditions maintained in these experiments. There seems to be some stimulus to the stomach caused by the hydrazine injections, which can hardly be secondary to liver damage, for we have observed many times that dogs begin to vomit within fifteen minutes after the injections. This cannot be observed in the rabbit, but stimulus to the gastric secretion does occur, as shown by the presence of considerably more free acid in the stomachs of our experimental animals than in the controls which have fasted an equal length of time.

SUMMARY

1. Injections of suitable doses of hydrazine into rabbits cause an increase in the CO_2 capacity of the blood and of the plasma.

2. This increase in CO_2 capacity of plasma is approximately equivalent to the increase in total fixed base of the serum.

3. An increase in the base to chloride ratio of the plasma suggests an actual increase in available base.

4. The increase in free acid in the stomach may account for the increase in available base in the plasma.

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REVIEW OF CERTAIN COMMUNICABLE DISEASES IN TEXAS TRANSMITTED BY ARTHROPODS

LUDWIK ANIGSTEIN*

The great variety of natural features of the State of Texas, the climatic differences in its various regions, the diversity of its soil, vegetation and fauna, offer an exclusively wide range of environmental factors. The complex physical geography of the State extending from the pines in the north to the palms in the south provides a rare panoramic setting in which problems of geographic correlation are displayed and shaped by nature. Among these problems, communicable diseases, being largely functions of environmental factors can be interpreted from the viewpoint of medical geography. In this regard, the environmental variety of Texas—the scene of manifold physical factors offers an almost unique background.

Owing to the marked contrasts in the climatic conditions prevailing in various portions of the State the medical geographer will find a rare opportunity of studying not only the diseases of the temperate zone but also those peculiar to warm climates.

I. MALARIA

In analyzing the distribution of tropical diseases we will find that many of them are not strictly confined to the tropics but also occur in the temperate zone although in a moderate intensity. Malaria, for instance, occurs in Northern United States and Northern Russia; however, it never assumes in these latitudes large proportions. On the other hand, the closer to warm climates, the higher the incidence of this disease will be. This can be readily explained by the fact that the moist heat is particularly favorable for breeding mosquitoes—the transmitting agents of malaria. This fact, also true for other diseases transmitted by insects, is strictly connected with the life habits of the vectors which require moist heat for their propagation.

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Malaria is certainly the most prevalent and most destructive infection in the world where millions of inhabitants of the warm climate suffer from the disease. Owing to its chronic course frequently extending over a period of years and the debilitating effect on the patient, it may assume in malarious communities the rank of a social disaster. Although the primary factor responsible for the spread of malaria is the presence of a suitable mosquito, other secondary factors cannot be underestimated. It is a known fact that a low standard of living in insanitary conditions will enhance the breeding possibilities of mosquitoes. Besides, poor economic conditions and malnutrition will attenuate the resistance of the population and aggravate the malaria in a community. For these reasons the malaria problem in many instances has to be attacked from various angles, including the economic and social approach.

General Malaria Situation in the United States

Malaria is a wide-spread disease in the United States, where at least 36 States are affected. These include all of the southeastern States, a large portion of Texas and Oklahoma, Missouri, Louisiana, and Florida, to mention only the most heavily affected. It is chiefly the disease of the rural population which is the most exposed to mosquito bites. As in any malarious area, the economically lower strata of the inhabitants constitute the majority of the infected population. This is not only related to the financial factor—the inability to pay for adequate food and treatment, but also to the lower standard of living including a poor and primitive type of housing which offers suitable shelters to mosquitoes. Judging from the official records about one million cases of malaria with 5,000 deaths are reported annually in the United States of America. No definite answer can be furnished as to the factors which gave rise to the wave of 1935 and to the following decline in 1938. One fact deserves attention, namely, the peak of malaria morbidity and the increased death-rate in 1933–1936 all over the South occurred at a time of economic depression, while in the following years more food was provided and more funds were available for treatment. At present, however, the malaria morbidity curve points upward again.

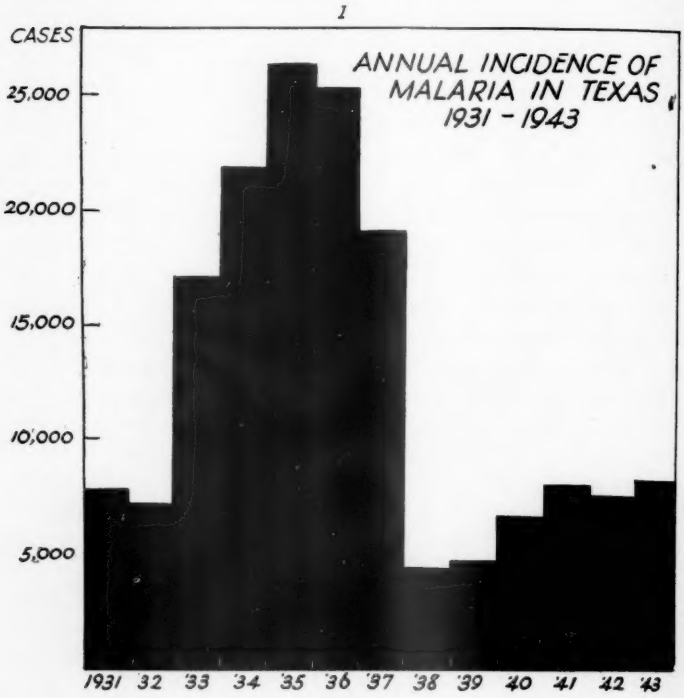
The Incidence and Distribution of Malaria in Texas

Generally speaking, the statistical data on the true incidence of malaria in a given area are frequently not reliable. This is due to the fact that the clinical diagnosis of "chills and fever" cannot be relied on as a sufficient criterion even in typical cases, unless it is confirmed by the identification of the malaria parasite by blood examination of the patient. However, this procedure is not frequently used by the practicing physician, who in many instances relies on the self-diagnosis of the patient. These cases are accordingly treated with antimalarial drugs without adequate diagnosis.

The statistical data on the incidence of malaria in Texas based on the morbidity reports have to be, therefore, evaluated with the above provisions. Whatever the error, we may assume that the actual number of cases is higher than recorded, due to the frequent self-treatment of malaria patients, without consulting the physician, and also to the fact that no reports are being received from many counties. The annual incidence of malaria in Texas for the period 1931–1943 shows an abruptly high level during the years 1933–1937 with the peak of 26,304 cases reached in 1935. This unusually high level was followed by a rapid decline to 4,400 cases in 1938 but beginning with 1940 an upward trend of the chart is noticeable. The number of cases exceeded 8,000 in 1941 and was still rising in 1943 with 8,265 cases reported (Chart 1).

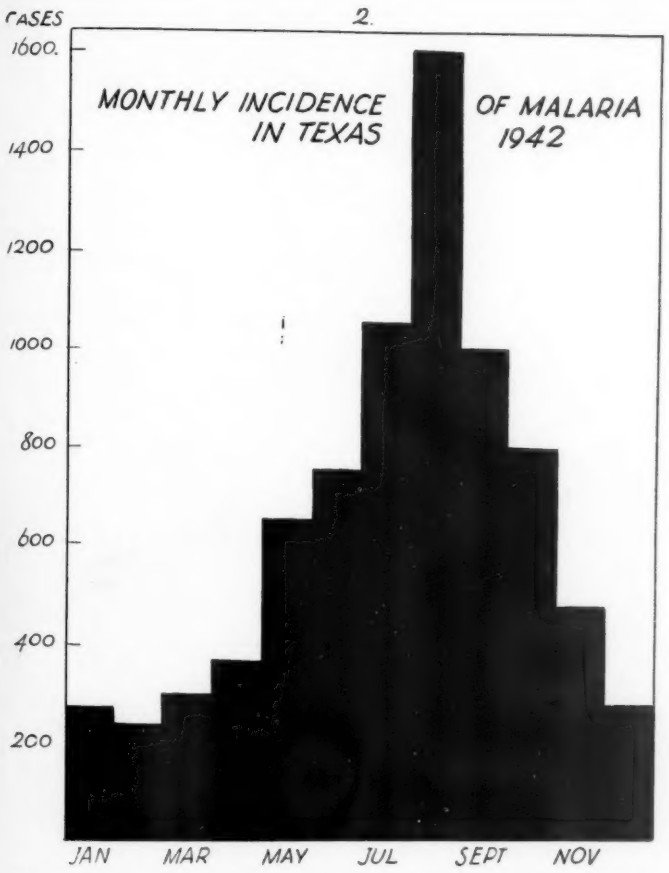
Any attempt to interpret the actual causes of the waxing and waning in the incidence of communicable diseases has usually a speculative character. While it is possible that the increase of malaria in 1933–1937 was a part of the cyclic phenomena also known for other infectious diseases the steadily declining mortality rate might be due to the improving economic conditions. That such cycles actually occurred in the past was shown by Faust (1943) in a retrospective analysis of malaria morbidity in the United States, where the cyclic peaks in 1915, 1921, and 1933–1935 are significant. The belief was also expressed (Dauer and Faust, 1936) that a new rise is due in 1940, a prediction which proved correct in the heavy areas of endemicity including Eastern Texas (Chart 1).

1



Whatever the natural march of malaria might be, the disease "is by no means a static problem . . . it is continuously changing in intensity either from year to year or in geographical distribution. Spontaneous disappearance is observed in some marginal zones, and the introduction of man-made malaria is reported in other regions" (Deutschman, 1943).

It is known that malaria is a seasonal disease, its highest incidence coinciding with the summer months in the temperate zone or with the rainy season in the tropics when the mosquito activities are at their height. The greatest number of cases in Texas are reported from June through September with the highest figures reached in August (Chart 2). However, malaria occurs in Texas all year around subsiding in winter months to about one-eighth of its incidence in August.



It is always an ominous sign when a seasonal disease shows an increase at the normally quiescent period. Judging from the recent reports of the State Health Department a sudden and unusual increase of the disease occurred in the early winter season of 1944, when 150 cases were reported during one week of February, exceeding four times the average. The most affected counties were: Bell, Collin, Franklin, and Mills. It remains to be seen whether these cases were recrudescenses

of chronic infections or, what seems more likely, were imported from the outside.

Wherever malaria occurs, its distribution is correlated with the physical geography and natural history of the locality. We may, therefore, expect that in Texas which on the basis of its physical geography can be divided into clear-cut natural regions (Johnson, 1931, see Map A) the prevalence of malaria

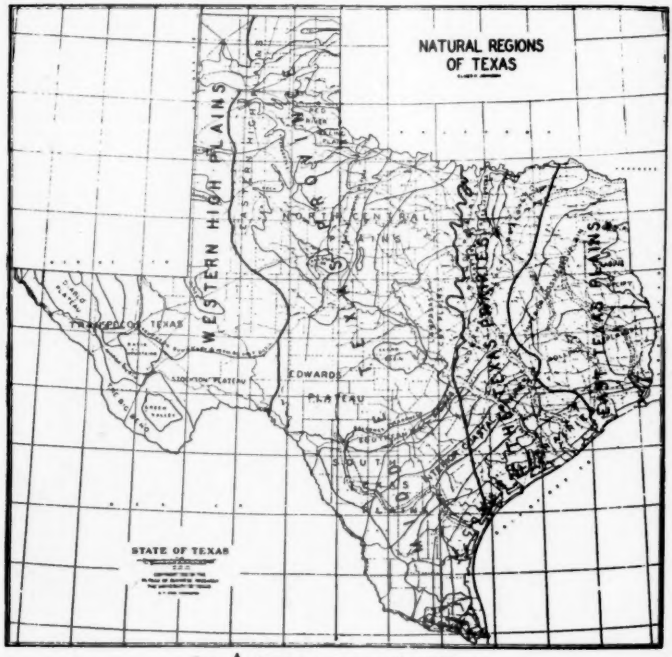


FIGURE A General Key-Map of Texas Natural Regions.

will also differ in various portions of the State. Moisture (rainfall) as the main climatic factor which determines the physical aspect, and the fauna and flora of the various natural regions is also of influence on the mosquito population. Under suitable conditions the anopheline mosquito will breed in abundance and may transmit malaria from infected persons to others. The more human carriers of the malaria parasite are present in a locality, the more fresh infections can be expected.

There are several anopheline species carrying malaria in Texas, the most important being *A. quadrimaculatus*, the predominant species in the Southern States. Among other malaria vectors in Texas, one deserves attention. This applies to *A. albimanus* which is principally of tropical distribution and is known as a mosquito of hot, humid climates, where it breeds in a great variety of water collections, either fresh or brackish, in lakes, backwashes of streams, swamps and pools. It is the most important malaria vector in the West Indies and Central America including Panama and in northern South America.

It is of interest to note that in the United States *A. albimanus* is known to occur only in the lower Rio Grande Valley of Texas. It was first found in Brownsville, Texas, where it is apparently limited to Cameron and Hidalgo counties. Other examples could be quoted as to the occurrence in Texas of some invading arthropods (e.g., the tick *Amblyomma cayennense*) which are indigenous to tropical America. This biological phenomenon affords an additional touch of the tropics to the complex medical geography of the State.

In the Western High Plains of Texas where moisture and rainfall are at the lowest the incidence of malaria is low judging by the sporadic cases reported. In following the natural regions from the high elevations with less rainfall down to the humid East and Southeast we find the malaria incidence on the increase. This is true for the Coastal Prairie where malaria is more prevalent, but its incidence is particularly high in the East Texas Plain parallel to the Louisiana border. Most of the cases are reported from counties adjacent to the Red River with 1,263 malaria cases in Lamar County in 1943. This section includes the most humid region where the annual rainfall ranges between 40 and 45 inches (compare maps B and C). From the viewpoint of high humidity this region (east Texas plain) is unlike the rest of the State (Johnson, 1931). It is mostly an open and rolling country with dense vegetation and pine forests and abundantly irrigated by streams and creeks which frequently form pockets of stagnant water and marshes. In addition, the wide bed of the Red River and the low portion of the Sabine River provide the adjacent areas with numerous water collections. These natural hydrographic

features offer obviously ample opportunity for mosquito breeding. The general economic status of the chiefly cattle raising population is poor, the standard of living low, a situation so frequently met with in malarious countries. The primitive type of housing sheltering mosquitoes brings them into close contact with the inhabitants.

Experience gained in various malarious countries brought enough evidence that human habitation is a factor of primary importance in the acquisition and spread of malaria. The fact that the anopheles mosquitoes are mainly househaunters and night biters explains the existence of known "malaria houses" where inhabitant after inhabitant acquires malaria. These houses usually possess poorly ventilated, dark, dirty and damp

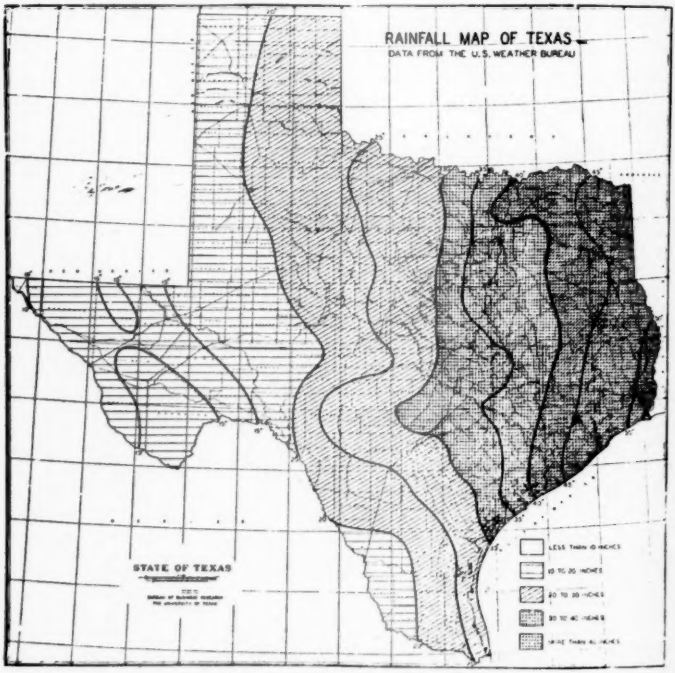


FIGURE B. Mean (Average) Annual Rainfall Map of Texas.

portions which are preferred by mosquitoes for their hibernation.

Consequently, the above natural as well as the man-made environmental factors fulfill the basic requirements necessary for a high prevalence of malaria. In fact, the total of malaria cases reported in 1943 from the 37 counties of the East Texas Plain amounts to 5,438, leaving about 3,000 cases for all the rest of the State.

An attempt was made to analyze the situation in the individual counties of the East Texas Plains. The last census of the rural population only, the most exposed to malaria, was taken in account and the morbidity rates were calculated from the reported malaria cases.* The figures thus obtained showed a malaria morbidity rate per hundred thousand population as

*By courtesy of Dr. J. Allen Scott, Associate Professor of Statistics and Epidemiology, The University of Texas, Medical Branch.

high as 38.7 in Lamar County, 26.2 in Cass County, 22.3 in San Jacinto County, and 10.4 in Orange County. The average malaria morbidity rate of the entire region (total rural population 859,000) amounts to 6.33 per hundred thousand, the lowest rate being 0.1 in Galveston and Nacogdoches counties.

It has been mentioned before that the reporting of malaria in the State is far from satisfactory in many respects. This applies first of all to the identification of the malaria parasite by blood examination. This procedure is, however, not frequently and not always properly used by the medical practitioner, particularly in the more remote rural areas where laboratory facilities are absent but where malaria is prevalent. It is obvious that the finding of the malaria parasite in the patient's blood is essential not only for the individual diagnosis but also for the administration of the proper treatment.

From the public health angle, the evaluation of malaria intensity in a community can be judged from the rate of children showing an enlargement of the spleen due to malaria (splenic index). The higher the index, the higher the endemicity of malaria. These essential data are as yet not available in the State.

The control of malaria is under the jurisdiction of the State Health Department and is carried out in coöperation with city and county health organizations. Since 1942 when the United States Public Health Service inaugurated the program of malaria control in areas of military concentration and essential civilian war activity Federal funds were made available and the effort has been increased. Lately, malaria in the State as a whole began to increase, possibly due to the mysterious causes influencing the "natural" cycles of diseases. If the spectacular reduction of malaria in Texas as well as in other States during 1938–1942 as compared with the preceding period was coincidental with the declining phase of a cycle, then its interpretation as the result of malaria control measures would be at least premature.

Whatever the causes of the variations in the intensity of malaria might be, the migration of people, particularly the mass influx of newcomers to malarious areas some of which cover the expanding war activities should be considered as a

serious factor which may enhance the indicence of the disease. In addition, the presence in this country of war prisoners from Africa and the return of our troops from the tropics will add malaria carriers which might spread the infection and aggravate the situation. Under these circumstances, the introduction of an exotic strain of malaria parasite may start an epidemic of this foreign type of malaria among a susceptible population.

Summary and Recommendations

The above review of the malaria situation in Texas is far from complete. It is merely an attempt from the available and rather fragmentary data to gain a general impression of the malaria situation in the State. It has been shown, however, that the malaria problem of the East Texas Plain covering an area of about 30,000 square miles and populated by about one million rural inhabitants deserves full attention. It would be premature to make specific suggestions as to the application of appropriate anti-malarial methods before the situation is thoroughly investigated on the spot.

For this reason a *scientific study* of malaria should be inaugurated and continued *in the laboratory and in the field.* The purpose of these studies is first to ascertain the relative importance of the disease as compared with the significance of other coexistent diseases and conditions which affect the health of the population. The establishment of this fact would then enable us to suggest appropriate measures and expenditure. We can, however, anticipate that we would not be concerned with the problem of converting a malarious region into a malaria-free area. In this regard, the history of special and large-scale anti-malarial campaigns is (with very few exceptions) chiefly a record of exaggerated expectations followed by disappointment and abandonment of the work. However, we may consider as a great achievement if malaria will cease to be an important cause of sickness and death.

It is obvious that the suggested study of the local conditions will be greatly handicapped by the limited staff equipped with special training. It would be within the responsibilities of The University of Texas to provide such a staff which under an

expert leadership would carry out investigations in the field and provide the necessary material for further elaboration and *research.* It would be necessary to educate *malariologists* who would attack the problem from various angles. The term "malariologist" is not limited to medically-trained persons because malaria as a public health problem cannot be dealt with from the purely medical standpoint alone. It requires a collaboration of *epidemiologists* and *medical entomologists* specially trained in the knowledge of the biology and habits of mosquitoes and their identification. The malariologist and his team will be mainly concerned with field work in rural communities carrying out malaria and anopheline surveys in order to locate the actual and potential danger of infection. The data thus obtained will then serve as a basis for the elimination of breeding places of dangerous anophelines revealed by the above surveys. This phase of the program will be followed by advice and collaboration of *sanitary engineers* specialized in drainage and in the study of soil properties.

The role of the *medical practitioner* in controlling the manifestations of malaria is very significant, provided he is trained in this particular line. Such special training in the diagnosis and treatment of malaria could be provided by the respective units and departments of The University of Texas. These specialized practitioners would then serve as part-time "malaria officers" responsible to the respective county health officers. The activities of the "malaria officers" will be greatly enhanced by inducing persons who, ordinarily, do not consult a doctor until they are seriously ill to do so at an earlier stage. There are many untreated malaria carriers who greatly contribute to the spread of the disease.

In addition to post-graduate courses in malariology for physicians *medical technologists* should be trained in hematology and in practical diagnosis of the malaria parasites.

Since the program of malaria control is a community problem requiring full coöperation of the people, its success largely depends on *education.* The community should be educated as to the basic facts on malaria and informed about its danger and means of prevention. Special courses of instruction should be offered to the principals and the teaching staff of public

schools, junior high schools and high schools. These trainees will then disseminate the acquired knowledge among their own community and expand the interest of the people from the local malaria problem to the spirit of public health. The teaching of the various phases of health and disease should begin with the public school where the young generation inspired by their masters will greatly contribute to the promotion of the Nation's health.

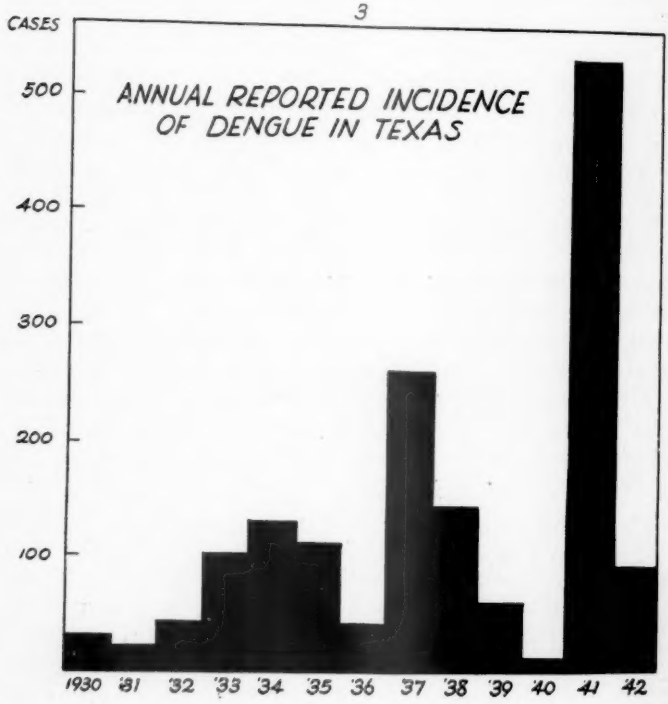
II. Dengue Fever

This disease also known under the name of "break-bone" fever is another member of the group which is carried by mosquitoes. Contrary to malaria which is, practically speaking, rural in distribution, dengue is a typical urban disease. This is due to the fact that the carrier (Aedes egypti) is a domestic mosquito which unlike the malaria anopheline mosquito shows a strong preference for breeding in water contained in artificial receptacles in or near human habitations, such as barrels, cisterns, gutters, unused plumbing fixtures, basins, tin cans, or other accidental collections of water. A very small quantity of water, which will remain for a week or ten days is sufficient for development of this mosquito. *Aedes egypti* requires warm climate and is found within the limits of the latitude 38° N. and 38° S. The geographical position of Texas and its climate within the coastal area fulfills these requirements to full extent. This mosquito is very prevalent in the towns and cities of the Gulf Coast and presents, therefore, a potential danger for the spread of dengue. It is also the same mosquito which transmits yellow fever, now limited to certain areas of the tropics, but in the past decimating the people of Texas.

Dengue fever is a mild disease as far as very low fatality rate is concerned, but it is a very debilitating disease which in the case of extensive epidemics may paralyze the life of a community. Such an epidemic occurred in Galveston, Texas, in the summer of 1922 and raged there for a number of weeks. From Houston the disease spread to all parts of Texas. The number of cases in the state has been estimated at about 600,000. In Galveston there were probably not less than 30,000

cases, in Houston 30,000, in Dallas 20,000. The average cost per case for medical attention can be estimated at $3.00; in addition to this there was an average loss of time of seven days in every case. For the entire state the loss from the epidemic can be estimated at $1,500,000 plus 3,750,000 lost days. Had it been yellow fever instead of dengue that the Aedes was spreading, the death-rate would have been disastrous (Rice, 1922).

Since that time sporadic cases of dengue have been reported in the State with 257 cases in 1937, and an attenuation for the following three years. Then suddenly in August, 1941, it became evident that dengue reports were accumulating in the lower portion of the Rio Grande Valley (Chart 3). An investigation of the State Health Department revealed a seri-



ous epidemic in Hidalgo and Cameron counties. While over 500 cases were reported during 1941 it is estimated that no less than 2,000 cases had occurred in Hidalgo County. Later in October the disease moved up the Rio Grande Valley to the Laredo, Eagle Pass and Del Rio area (Annual Morbidity reports, Texas State Department of Health, 1942).

The origin of the 1941 outbreak of dengue is obscure, but sporadic cases are reported every year and serious epidemics like that of 1922 may break out at any summer season in *Aedes egypti* infested communities.

The danger of reintroduction of yellow fever to this country is ever increasing with the changing picture of transportation. The greatest danger has come with the airplane. Until a few years ago travel between South America and the United States was possible only by steamship, while today by air passage an infected mosquito or infected person may be brought to this country overnight being accessible to many Aedes mosquitoes before any evidence of the disease appears.

Control: The State Health Department is carrying out a large scale control of the Aedes mosquito particularly along the Gulf Coast in conjunction with the U.S. Public Health Service.* The control of dengue and of yellow fever is based on the application of mosquito control measures and should be carried out in the following lines:

1. Elimination of all water holders and artificial containers about a premise. This should be enforced by a cycle of house to house inspections.
2. Containers which cannot be destroyed because of their use are inspected every ten days and the water surface sprayed with oil.
3. Rendering of cisterns and rain barrels mosquito proof by adequate screening.

This as any other public health problem requires in addition to funds the full coöperative effort of the community which can only be expected when the necessary educational efforts are made by ourselves.

*Professor A. C. Chandler, Rice Institute, Houston, special consultant, U.S. Public Health Service, is in charge of the program.

Preliminary surveys and epidemiological investigations of the area under control will limit our activities to the potentially dangerous foci and will consequently save unnecessary expense.

There are still some mysterious, unexplained factors which govern the appearance of dengue and of other mosquito-borne diseases which problems can only be solved by continuous and concentrated research.

III. Typhus Fever

General Considerations

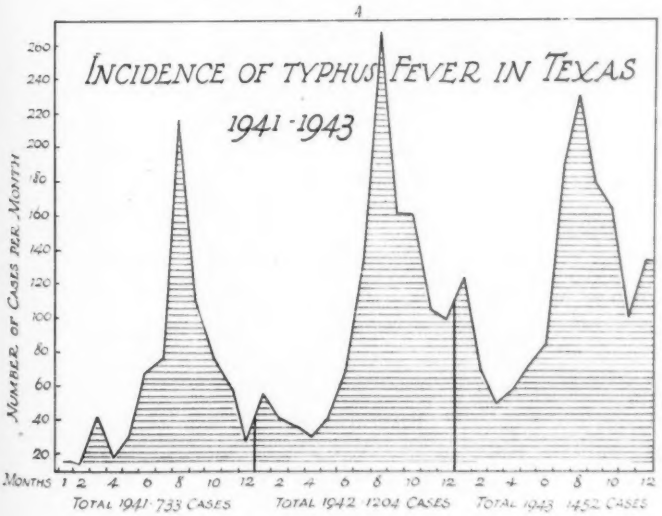
Under the name of typhus fever two varieties of the disease are considered; one is transmitted from man to man by the human body louse, while the other is carried to man by the rat flea from infected wild rats. The first, also called epidemic typhus, is liable under certain conditions, such as lack of personal hygiene, over-crowding, filth and famine to occur in extensive epidemics. For these reasons louse-borne typhus always has been a faithful companion of wars. The flea-borne typhus, on the other hand, is correlated with all the factors leading to direct or indirect contact of man with rats and may occur in any social community at any time. However, environmental factors, particularly primitive and defective housing accommodation, negligence in garbage disposal and unprotected food will attract the rats to human habitations and increase the danger of infection. While louse-borne typhus is prevalent in the temperate zone where it occurs in winter, murine typhus is mostly endemic in the warm climates with the highest incidence in the summer, when the rat population and infestation with fleas are the highest. Another point of distinction is the high mortality rate of the louse-borne typhus (10–15%) as compared with the low death rates from murine typhus (3–5%).

Distribution and Incidence of Murine Typhus in the United States

The geographical distribution of typhus is mainly confined to the southeastern states especially those bordering the Gulf of Mexico. In the past the disease was practically limited to

towns, along the southern Atlantic Coast from Baltimore south and then along the Gulf Coast up to the Rio Grande. Towns in the interior of the southern states were affected to a much lesser extent. For the last decade, however, a geographical extension of the disease took place with a definite shift to rural areas. This occurred in Alabama, Georgia and Texas and was probably due to the changing agricultural practices, namely, to the recent increase in planting food crops. This resulted in the storage of food which in turn attracted rats from towns.

The most heavily infected area involved the southern part of Georgia, the southeastern part of Alabama, the northern part of Florida and southern and eastern Texas. In Texas the typhus area has extended throughout most of the southern and eastern parts of the state and has now reached the Oklahoma border. Although large cities in Texas (Austin, Dallas, Houston) are affected by typhus, its highest incidence includes small towns and villages. The most important factor responsible for keeping the disease alive in nature is the gray rat, but other rodents, particularly the field mouse may also play a



conspicuous part as reservoirs of the infection. The infection to man is carried from these rodents by the flea either through bite or by direct contact with the flea feces.

Murine typhus is primarily a disease of young and middle-aged males who while working in the store or on the farm are more exposed to the infection than women. It is apparently an indoor disease, originating in shops, grocery stores, granaries and warehouses, and occurs in rat infested households. It appears to affect mostly the middle class and the lower social strata.

Murine typhus prevails in the southeastern states all year around, but it shows a definite seasonal incidence. In Georgia the number of cases rises gradually from March to the summer months with July, August and September as peak months of the year. A similar trend of the typhus curve is noted in Texas, where the peak is reached in August declining in September (see Charts 4 and 6).

As to the prevalence of murine typhus in the United States the first reliable reports were registered about 20 years ago when physicians had become first conscious of typhus and cases were recognized. In 1925 about 150 cases were recognized and reported for the United States; 510 cases were reported in 1930 and 955 in 1932. As can be seen from the chart (5) the incidence curve fluctuated around one to two thousand cases annually until 1939 when a rapid increase of typhus morbidity took place ending with the alarming figure of 4,517 cases in 1943. As we shall see later, Texas' contribution to the bulk of typhus cases in the United States is very conspicuous.

The Incidence and Distribution of Typhus in Texas

It would be merely a matter of speculation as to how long typhus fever has been endemic in Texas. However, Nixon (1936) in his "Century of Medicine in San Antonio" refers to it as occurring in the Spanish era of the late 18th century. The disease seemed then to occur in large epidemics, decimating the population and the neighboring Indian tribes. Judging by the extent of the epidemics and by the large number of deaths, it would seem that the disease was of the

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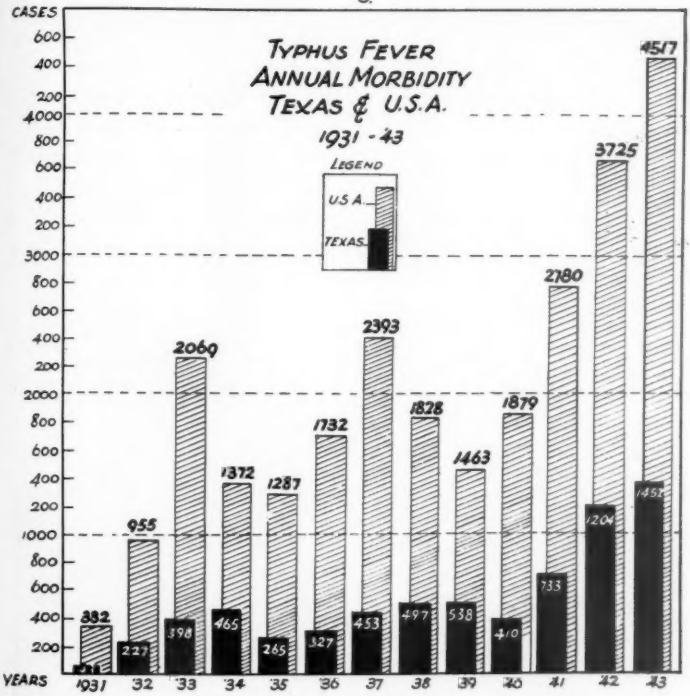
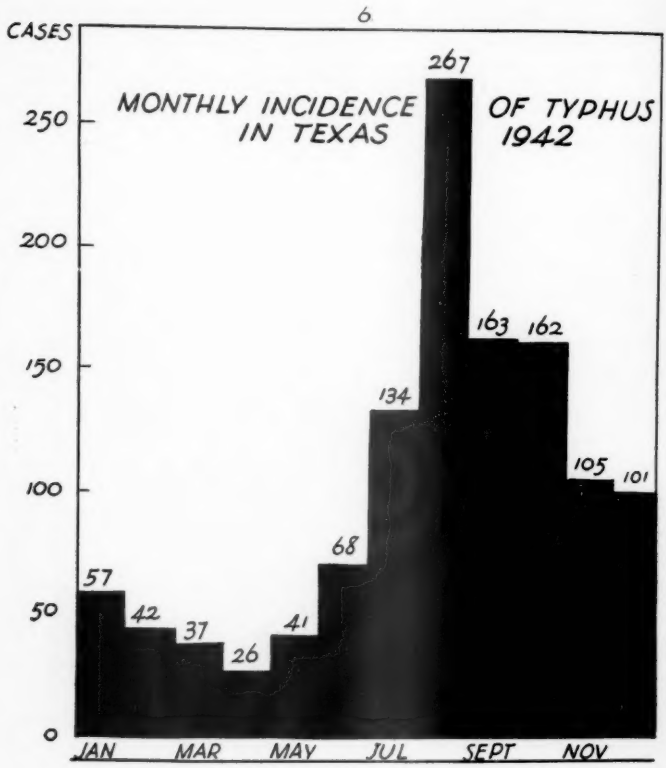


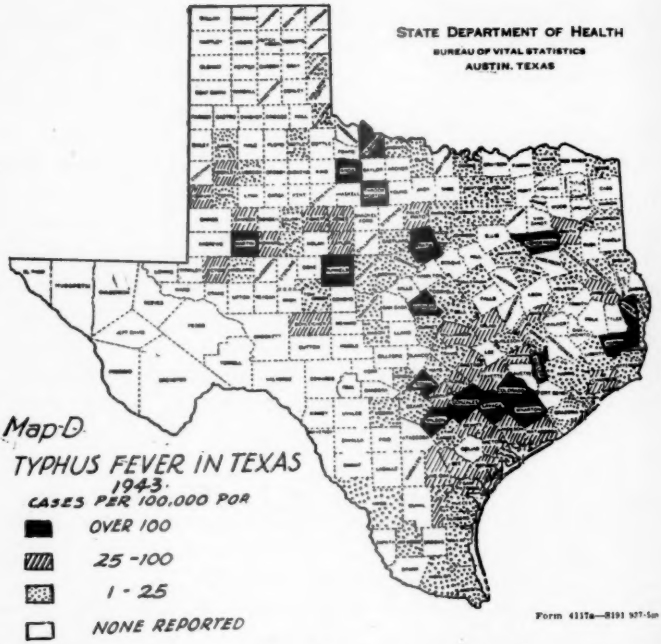
louse-borne type. Another epidemic wave of typhus swept San Antonio, New Braunfels and Fredericksburg in 1840 (Kemp, 1939). Undoubtedly, typhus has existed ever since in Texas, but it was not until 1915 that the outbreak in Laredo gave more accurate information about the disease. The worse outbreak occurred then in El Paso with 55 cases and 9 deaths. While the above cases were most probably louse-borne, the five cases reported by McNeill (1916) from Galveston were of the murine flea-borne type. Later 70 cases of the same type were reported in the lower Rio Grande Valley. Although there were several mass outbreaks of louse-borne typhus in Texas this type of the disease has never gained a foothold in Texas. At present, we are concerned in this state with the flea-borne typhus only.



With regard to geographic occurrence of typhus within the state, our data depend entirely on the cases reported to the State Health Department. It is true that for the past years and, particularly during the war period great attention is being paid to typhus at the combat zone as well as on the home front, and it is safe to assume that the recognition of cases is improving all over the country. However, in a number of cases, particularly in children in whom the disease usually runs an atypical and mild course or may be mistaken for some of the infections of childhood typhus may be missed. In these cases, a great help in the diagnostic is the blood test (Weil-Felix

reaction) which is not sufficiently enough used by the physician. Consequently, with all due respect, the reporting of the typhus cases is far from what it should be. No reports of typhus were submitted by about 50% of the counties in 1943, but it would be unsafe to conclude as to the actual absence of the disease in these areas. Recent records show sporadic cases in the western high plains, where typhus was previously absent or at least not reported, while in the vast and sparcely populated regions of Transpecos and in the Edwards Plateau it is conspicuously absent. Otherwise, cases are scattered all over the State with a definite and heavy accumulation of the disease in the thickly populated eastern and southeastern parts of Texas, where the typhus morbidity rates range between 25 to 100 per 100,000 population. The central and lower Gulf Coast area centered around Lavaca, Gonzales and Fayette counties, the lower east Texas with center at Houston county; central west Texas in the Big Spring community is also very active. Other areas of activity are: Tarrant, Jones and Jefferson counties. Only sporadic cases were reported lately from the lower Rio Grande (see Map D).

As mentioned above the general trend of typhus is its expansion from large cities to small towns, villages and to rural areas—a fact also noticed in the states of the South (Georgia). In this respect, a small rural community (population about 3,000) in Lavaca County, Texas, may illustrate this statement. In this small town 165 cases of typhus were reported during three weeks of August in 1941—an unprecedent event in the usually sporadic on endemic character of murine typhus. This mass outbreak of epidemic character coincided with the harvest season which was probably responsible for the accumulation of rats or has exposed the farmers to the infection from field mice. The still active typhus focus in Lavaca county contributes seriously every year to the bulk of reported cases and was almost entirely responsible for the peak reached in August, 1941 (see Chart 4). This chart also shows the general upward trend of the typhus curve as well as the clear-cut seasonal incidence of the disease. A significant and ominous feature is the rising level of typhus morbidity during the



"quiescent" winter months with 130 cases in December, 1943, exceeding about 4 times the seven year median for typhus in Texas. The upward tendency of the typhus curve in Texas begins with 1941 when 733 cases were reported as compared with 410 cases in 1940.

For the past three years Texas has continued to be the scene of a spectacular increase in the incidence of typhus reaching in 1943 record figures (1,452 cases) in modern Texas history. Ominous is the high incidence in the past two winter seasons which foreshadows a new, still higher wave in summer (Chart 4). The increased typhus morbidity also noted in the South obviously reflects on the typhus statistics in the United States where the number of 2,780 cases of 1941 rose to 4,517 in 1943. Of these more than 30% were contributed by Texas (Chart 5).

Typhus fever in this country is generally believed to be a mild disease with a low mortality rate of from 1 to 3 per cent.

However, more deaths from this disease are being reported lately with a death-rate reaching about 5%. It is quite possible that with the increasing number of cases, the disease is assuming a more virulent form.

Control of Murine Typhus and Recommendations

It is obvious from the foregoing that typhus is becoming one of our major health problems, which already has called full attention of the health authorities of the State. It is also clear that since the disease is contracted from infected rats and fleas, the control of the disease should be concentrated on a systematically maintained anti-rat campaign. However, rat extermination by poisoning and trapping can be regarded only as a temporary measure. A general anti-rat campaign as spectacular as it is in killing large numbers of rats may be regarded only as an emergency measure in outbreaks of typhus; in these cases it may actually relieve the situation. To control typhus by this means, it must be repeated every few months until permanent control measures are established.

In order to eliminate all the factors which may attract rats to human habitations garbage control and its proper disposal as well as clean-up of premises are essential parts of typhus control. The removal of rubbish and of all unnecessary objects around the household which otherwise would serve as hiding and nesting places for rats should become a routine. The most radical and permanent measure of typhus control is rat proofing of premises, which if effective is the radical separation of man and rat. (Roy J. Boston, 1940.) Old unprotected and rat infested premises and buildings should be regarded as dangerous potential foci of typhus. By adequate rat proofing the access of rats to these houses would be eliminated. This long-term program which lies within the responsibilities of municipal and county health administrations requires special teams of workers and the guidance of sanitary engineers. Such a program mainly based on the lines originally adopted by the State of Georgia has been recently inaugurated in Texas by the U.S. Public Health Service in collaboration with the State

and local health administrations of several large cities: Austin, Houston, Dallas, Fort Worth, and Corpus Christi. The rat proofing scheme (rat stoppage) carried out under the guidance of Government experts is, however, considered as a temporary participation of the U.S. Public Health Service with the provision that the work will be eventually taken over by the local health authorities. We have to be, therefore, aware of training the necessary teams of experts, particularly sanitary engineers, should the results obtained and the investment placed not be wasted.

Such a control program should be obviously preceded by preliminary local investigations of epidemiological character as to the determination of the main foci of danger in the community. Simultaneously, research work should proceed in order to investigate the nature of the infective agent. These activities should be accompanied by an intensive educational program of the population as a prerequisite of a successful campaign.

IV. Spotted Fever

In its manifestations this communicable disease is related to typhus but is much more severe and highly fatal. It is not directly contagious but infects man through the mediation of a tick. Ticks which are parasites of various animals (cattle, horses, dogs, rodents, etc.) keep the infection alive in nature and by biting may transmit the infective agent to man. The disease is known in the United States particularly in the mountain states, from where it spread east and south. The total number of recorded cases amounts annually to about 1,000 with an average mortality of about 15 per cent. However, in many instances the death-rate was as high as 90 per cent.

In Texas several cases were recorded on the coast and one in Dallas since 1931. Recently, however, a small outbreak occurred in Brazoria County where four children were affected and two of them died. Investigations were carried out by The University of Texas Medical School and disclosed that the very abundant "Lone Star tick" in this area was responsible

for this disease. The outbreak occurred under special circumstances which serve as a perfect example to what extent the environmental factors may interfere with public health.

The two families involved belonged to war workers who came to a small community near Freeport, Texas, where the population has rapidly and greatly increased. Owing to the acute shortage in housing accommodation, the workers were compelled to live in trailers in an area densely overgrown by vegetation and heavily infested by ticks. The direct exposure to the ticks resulted in the fatal infection.

The *control of the disease* is difficult, the only measure would be destruction of the wild growing vegetation by burning out the grass and shrubs. Education of the people in warning them of the danger will certainly be of great help.

Some other diseases in Texas are probably transmitted to man by ticks or other parasites but these problems still remain to be solved by proper investigations. The cause of the above-mentioned spotted fever outbreak was disclosed through a systematic study by a *trained team of workers of The University of Texas.* It is only through further and continued encouragement of *research* that other problems of public health importance can be solved.

All data pertaining to the incidence of the diseases in Texas discussed in the present report including the charts are based on the information published in the weekly and annual morbidity reports of the Texas State Department of Health. The Public Health Reports of the U.S. Public Health Service were also consulted.

The material discussed here will be presented elsewhere in abridged form in association with Doctors T. V. Schuhardt and Gordon Worley of The University of Texas, Austin.

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NOTE

The Argasidae of North America, Central America and Cuba, by R. A. Cooley and Glen M. Kohls, June, 1944. The American Midland Naturalist, Monograph I: pp. 1–152, pls. 1–14, and 57 text figures. The University Press, Notre Dame, Ind. Cloth bound. Price 2.00.

This monograph, the first complete work ever to appear on the North American and Central American soft ticks, is a welcome publication, not only for the professional entomologist, but also for all interested in tick-borne infections. The authors (who are associated with the United States Public Health Service, Rocky Mountain Laboratory, Hamilton, Montana) had for study an abundance of material, mostly collected by staff members of the Rocky Mountain Laboratory.

Four genera are recognized, *Argas* Laterielle, *Otobius* Banks, *Ornithodorus* Koch, and *Antricola* Cooley and Kohls. The genus *Ornithodorus* contains 19 species, the other three genera contain 2 species each, making a total of 25 species. The genera and species keys are designd for both nymphal and adult charactrs as far as material permits. For each species there is given the bibliography and synonymy, a concise description of all the known stages, the hosts and distribution, a distribution map, line drawings illustrating the pertinent taxonomic characters, and, when known, notes on the biting habits and disease-carrying propensities of the species.

A valuable chapter is one on the Medical and Veterinary Importance of the Argasidae. Five species, all of *Orinthodorus*, are listed as proved vectors of relapsing fever spirochetes. These are *O. hermsi*, *O. turicata*, *O. parkeri*, *O. talaje*, and *O. rudis*. Experimentally, *O. parkeri* has been shown to be capable of transmitting Rocky Mountain Spotted fever and *O. hermsi* can transmit, under experimental conditions, both Rocky Mountain Spotted fever and American Q fever.

Other items which enhance the value of the monograph are a chapter on each of the following: Explanation of Terms, Principal Characters of Argasidae (with figures), Methods, Classified List of Hosts, Geographical Distribution of Species, and a Bibliography of five pages.

The authors are to be congratulated for making such a valuable contribution to the study of the Acarina. We fervently hope it may soon be followed by a similar monograph on the Ixodidae.

R. W. Strandtmann.

STATISTICAL STUDY OF SEVENTY CASES OF LEUKEMIA ADMITTED TO THE JOHN SEALY HOSPITAL, GALVESTON, BETWEEN 1921–1943

GWENDOLYN CRASS*

A study was made of the clinical records and necropsy protocols of all patients admitted to and necropsied in the John Sealy Hospital between the years 1921 and 1943, and having the diagnosis of leukemia. The purpose of this study was to determine if there were any correlating or causative factors to be found within such a group, and to compare the leukemias of this section of the States with similar studies made elsewhere, such as those made in the Johns Hopkins Hospital by Wintrobe-Hasenbush, and in the Huntington Memorial Hospital by Minot.

Tabulations include such factual data as age, sex, race, occupation, necropsy findings, as well as a comparison of the disease in childhood and adulthood. Wherever possible, these findings have been recorded in tabular form and determinations made on a percentage basis. Graphs are interspersed at intervals for clearer presentation of facts and figures. Only those cases were used which were considered by the investigator to be leukemia as judged from the reports of blood or bone marrow studies or from postmortem findings. All cases diagnosed as pseudoleukemia, incipient leukemia, or leukemoid reaction were excluded. The clinical reports were incomplete in many instances, and this must be considered in evaluating the data; also necropsis were not obtained on all patients having the disease, so that these cases must be regarded as incomplete.

Incidence: Of the total number of patients admitted to the John Sealy Hospital between 1921 and 1943, seventy had leukemia, representing 0.06 per cent. This is lower than is quoted for other comparable hospitals in similar studies. Thus, Kirschbaum reported an incidence of 0.86 per cent from the

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Cooke County Hospital in Chicago. It would be of interest to know if the incidence of leukemia is lower in the south than in the north, but evidence is not available for satisfactory judgment.

Is the disease increasing in frequency today? Such might be inferred from Table I, which shows a progressive increase

TABLE I

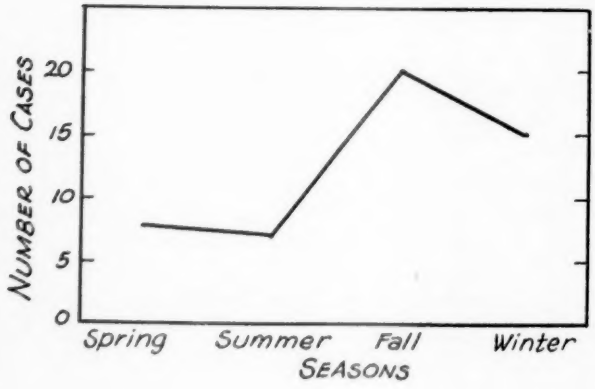
Number of Cases Admitted to The John Sealy Hospital Between 1921–1943

Year	Number
1921–1927	9
1928–1932	10
1933–1937	16
1938–1943	35

in the number of cases with each succeeding interval of time. However, there are limitations to this inference, namely, the increase in hospitalizations of patients in latter years, the improved hospital records, the better recognition of the leukemias, especially of the acute and aleukemic forms.

The relative proportion of myelogenous and lymphatic leukemia for the group as a whole is fairly evenly distributed

Figure 1.
SEASONAL DISTRIBUTION
OF THE ONSET OF LEUKEMIA



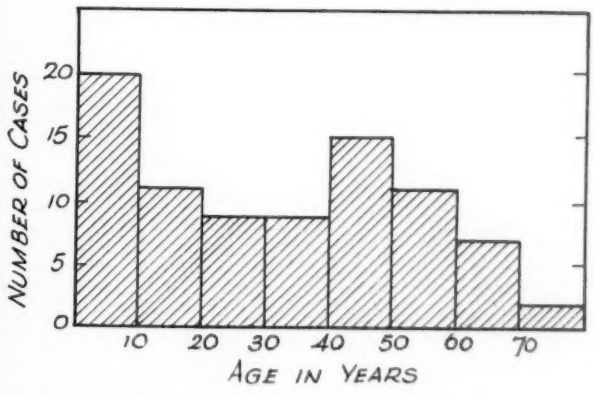
between the two conditions, there being thirty-three cases of myelogenous and thirty-seven cases of lymphogenous. These figures are in close agreement with those of Wintrobe-Hasenbush.

The possibility of leukemia having a seasonal variation was considered. This, however, is very difficult to determine with accuracy since the disease tends to have an insidious onset, and the patient is frequently not aware of the beginning symptoms. The onset has been considered from the time of the first symptoms developed that could be reasonably attributed to leukemia. Results plotted in Figure 1, show an increase in the disease during the fall and winter months. Children seem to be susceptible to the disease throughout the year, whereas, adults show a definite rise in frequency of onset during the winter months.

Age: Leukemia has no definite age boundaries, unless the lymphatic leukemias are separated from the myelogenous, and the acute from the chronic forms, in which case the disease has a tendency to fall within certain age periods. The total age spread in this series was from six months to seventy-five

Figure 2.

AGE OF ONSET OF LEUKEMIA



years. The greatest total number of cases recorded here, occurred before the tenth year of life, and there was another rise in incidence in the forty to fifty year age groups, as shown in Figure 2. A better picture of the disease is obtained if the leukemias are separated as to type and then plotted chronologically, as shown in Figures 3, 4, 5, 6. An analysis of the cases occurring before the age of twenty shows that acute lymphatic leukemia is the predominating form, only ten per cent being myeloid in type. After twenty years of age, chronic myelogenous becomes the more frequent condition until the sixth decade. A patient developing leukemia after sixty years of age is most likely to have the chronic lymphatic form. Can this be related to some metabolic process in the human body that would predispose the hematopoeitic system to respond differently at different age periods? Certainly the high incidence of acute lymphatic leukemia in childhood can not be relegated to a chance factor, nor can the sudden rise in chronic lymphatic leukemia after sixty years of age be totally disregarded.

Sex: The incidence of leukemia in relation to sex is different in the childhood and adult form of the disease. Before the age of twenty, the disease is equally distributed between males and females. In adulthood, leukemia becomes more common among males than females; this fact has been noted by various investigators who have reported their series in the literature. See Table II. Although there is some variation in the percentages recorded, there is almost a 2:1 ratio between the sexes.

TABLE II

Distribution of Leukemia Among Males and Females

Series	Myelogenous Leukemia		Lymphatic Leukemia	
	Male	Female	Male	Female
Leavell	60.0%	40.0%	72.0%	28.0%
Minot	56.0%	44.0%	74.0%	26.0%
Wintrobe	61.5%	39.5%	83.0%	17.0%
J. S. H.	70.0%	30.0%	66.5%	33.5%

Figure 3.
AGE GROUPING IN ACUTE LYMPHATIC LEUKEMIA

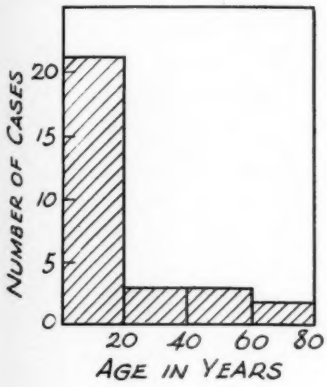


Figure 4.
AGE GROUPING IN CHRONIC LYMPHATIC LEUKEMIA

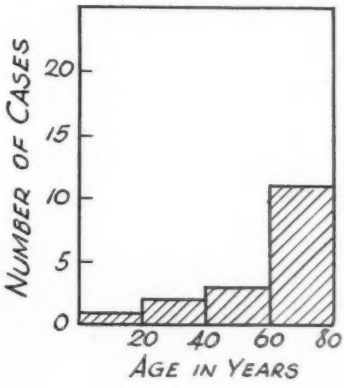


Figure 5.
AGE GROUPING IN ACUTE MYELOID LEUKEMIA

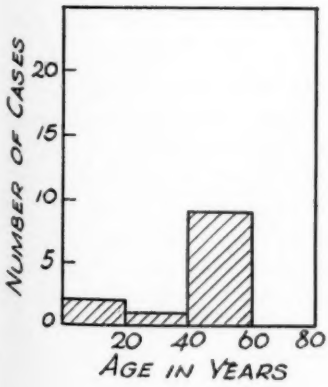


Figure 6.
AGE GROUPING IN CHRONIC MYELOID LEUKEMIA

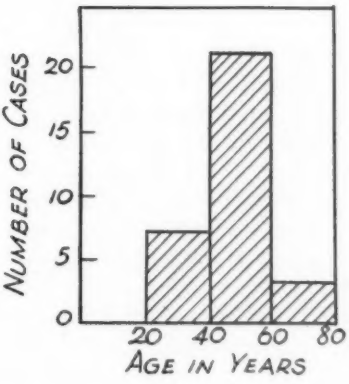


Figure 7.

COMPARISON OF THE INCIDENCE OF LEUKEMIA IN ADULTS AND CHILDREN

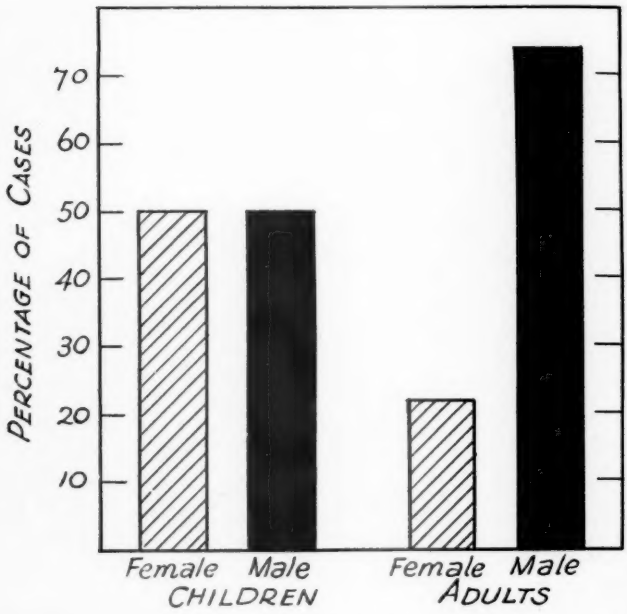


Figure 7 illustrates the difference in distribution. The fact that leukemia seems to take such a sharp drop in frequency for females after they reach adulthood, raises the question whether women may develop an immunity to the disease with sexual maturity.

Race: The admission rate for the negro is fairly high in the John Sealy Hospital: about forty per cent of the cases admitted on the medical service are colored patients. With the statistics compiled separately for the black and the white, there were some apparent variations in the disease for the two races. There were three times more white patients with leukemia

than colored. In the negro, myelogenous leukemia is more frequent than lymphatic by a 2:1 ratio, which ratio does not exist for the white. The colored patient tends to develop leukemia between 35–45 years, while the white shows a greater frequency for the disease in the 55–65-year period. Acute leukemias are more common in whites than in blacks. The negro lives longer after contracting the disease than does the white. The average duration of life for the negro with myelogenous leukemia was 28½ months; for the white it was 14½ months. The negro with lymphatic leukemia lived approximately 26 months after contracting the disease, whereas the white lived 18 months.

Occupation: Occupational studies gave no significant correlations. In this series of cases, the disease tends to affect those in the lower wage brackets, but it is not associated with any one occupational group, as noted in Table III.

TABLE III

Leukemia and Occupations

Barber	1	Mechanic	2
Bartender	1	Merchant	2
Cleaner	2	Porter	1
Clerk	1	Printer	1
Farmer	4	Salesman	2
Fisherman	1	Teacher	1
Housewife	8	Telegrapher	2
Laborer	11	Watchman	1

Clinical Course: The nature of the onset of leukemia is still an unsettled problem. The disease seems to manifest itself in slightly different complaints according to the type of leukemia. The patient with chronic myelogenous leukemia is most likely to consult his physician because of an enlarging spleen or liver, expressed by him in such terms as, "tumor in my stomach," "swollen stomach," "heavy stomach," or "pain in the side." The patient with acute myeloid leukemia notices symptoms more related to hemorrhagic tendencies, such as, "sore bleeding mouth," "bruise easily" or "blurring of vision." On the other hand, lymphatic leukemia has as its outstanding symptom fever; swollen neck glands and weakness are next

in frequency. Fever is especially prominent as the most pronounced symptom in children.

The symptomatology of leukemia may seem varied, but this has been explained according to the systems of the body involved. Associated with the elevated basal metabolic rate, the patient complains of insomnia, irritability, nervousness, and loss of weight. The lymphoid hyperplasia causes pressure symptoms of pain, cough, constipation, and dragging sensations in the abdomen. The dyspnea, weakness, and easy fatigue can be explained as a result of the anemia so often associated with this disease. Symptoms arise from the hemorrhagic tendencies, including bleeding gums, hematemesis and occasionally hematuria.

The past histories of these patients were not unusual. They all gave histories of the usual childhood diseases. There were a few exceptional cases, but these were not enough to be statistically significant. In one case, a woman had been a morphine addict for several years, and suddenly developed acute leukemia. In three instances, leukemia was manifest soon after a long debilitating illness, including tuberculosis, osteomyelitis and septicemia. Two cases developed after sulfanilamide therapy. There were two patients who gave histories of injury to the hematopoeitic system: in one, leukemia followed an injury in which the spleen was ruptured; in another, the patient had sustained fractures of the long bones on four different occasions. All of the above-mentioned conditions were found only in adults.

Syphilis was notably absent in this group of cases. Out of fifty serological tests for syphilis, only two were positive.

Physical examination revealed nothing outstanding in most instances. The patients were usually emaciated, pallid individuals with some elevation of temperature, enlarged nodes, liver and spleen, and occasionally hemorrhagic tendencies. Most often the diagnosis cannot be arrived at by physical examination alone, but requires a study of the blood smear.

Necropsy Findings: The necropsy protocols of all patients having a postmorten examination were studied for any significant facts. In all instances there was some enlargement of the liver and spleen. Chronic myelogenous leukemia caused

a greater increase in both liver and spleen than did lymphatic leukemia. There was a proportionately greater increase in the size of the spleen than in the size of the liver in all forms of the disease; that is, the spleen would often enlarge to ten times its normal weight, whereas the liver would be only twice normal size. There was no correlation between the age of the patient and the amount of increase in the spleen or liver. Females showed a relatively greater increase in the size of their spleens than did males.

It was interesting to note that in the microscopic reports on the acute leukemias, there was always an infiltration of all organs of the body with leukemic cells. On the other hand, in the chronic form of the disease, the leukemia infiltration tended to be limited to the liver, spleen and kidney; and the pancreas, without exception, was reported as normal.

Conclusions: Leukemia is a disease of low incidence, but may be increasing in frequency. A slight seasonal variation was found, with a rise in incidence during the fall and winter months. Leukemia is equally distributed between males and females before the age of twenty years, but is twice as frequent in males in adult life. Acute lymphatic leukemia is the predominating type before twenty years of age; there are no chronic leukemias of childhood. Chronic lymphatic leukemia becomes the leading type after the age of sixty. Myelogenous leukemia, both acute and chornic forms, occurs most often in the forty to sixty-year interval. Leukemia is more prevalent in the Caucasian than in the Negro race. Myelogenous leukemia is more frequent than lymphatic in the Negro race. The Negro lives longer after contracting leukemia than does the white. Leukemia is not related to occupations, and no factors were found in past histories that predispose to leukemia.

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A DIRECT STUDY OF INTESTINAL ABSORPTION OF CERTAIN SULFONAMIDES IN CATS*

(With a note on the hydrolysis and estimation of nicotinylsulfanilamide)

GEORGE A. EMERSON AND JACK K. FINNEGAN†

Many studies of the rates of absorption of sulfonamides from the gastroenteric tract of man and various animals have been reported. With the exception of a few incidental findings, these are based upon estimations of the sulfonamide content of blood or urine. A rough measure of differences in absorbability is obtained in this way, but the results must not be interpreted as a true measure of the permeability of the gastroenteric tract since the blood content of any agent given orally depends upon rate of excretion, rate of detoxication, permeability of the tissues, and other factors in addition to rate of absorption.

Direct estimation of the rate of disappearance of drugs from solutions injected into the lumen of the small intestine of animals yields a quantitative measure of the rate of absorption alone. A technique for this purpose has been perfected by Van Liere and has been applied in his investigations of the effects of anoxia on intestinal absorption of various substances. The present study utilizes this technique to compare directly the absorption from the small intestine in cats of sulfanilamide, sulfapyridine, Na sulfapyridine, 4-nicotinylsulfanilamide, sulfathiazole and sulfamethylthiazole.

EXPERIMENTS

Mature cats were starved 24–36 hours and narcotized with 220 mg./kg. of Na barbital given intravenously. The intestines were ligated at the ileocecal junction and again at a point 40 inches above, on the jejunum. Incisions were made at both

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points, the lumen of the loop was washed by slow injection of 50–100 ml. of 0.9% sodium chloride at 40°, and the intestine was lightly stripped to ensure quantitative return of the wash fluid. Double ligatures were placed at each end of the loop and a freshly prepared solution containing 0.040% of the sulfonamide in 0.9% saline was introduced at 40° until moderate distention was produced with about 20 ml./kg. A ligature placed below the point of injection was tied, the omentum replaced and the abdomen rapidly closed with Allis' forceps. Throughout, precautions were taken to avoid traumatizing the intestine or its nervous or vascular supply.

Twenty-five minutes later, the loop was removed after clamping off the mesenteric vessels, washed quickly to remove blood, and blotted dry. The residual fluid in the lumen was collected by opening the loop longitudinally for its entire length, and stripping. The volume recovered was measured to 0.25 ml. Blood was obtained intracardially, and oxalated.

Of the agents tested, only sulfanilamide and Na sulfapyridine were easily soluble to 0.040%. However, the other agents were completely dissolved before use by prolonged shaking and heating, and remained in 0.040% solution at 40° permanently. In no case did color appear in the solutions before use, although a brown tint developed in several kept 24 hours before they were discarded. None of the agents required the addition of base to produce solution. The pH of the various 0.04% solutions, as actually used at 40°, was: for sulfanilamide, 5.32; sulfapyridine, 5.29; Na sulfapyridine, 7.89; nicotinylsulfanilamide, 5.86; sulfathiazole, 5.60; and sulfamethylthiazole, 5.92.

The sulfonamide contents of aliquots of the residual fluid from the intestine and of blood were estimated colorimetrically in trichloroacetic acid filtrates by diazotization, treatment with buffered ammonium sulfamate and coupling with dimethyl-a-naphthylamine. For nicotinylsulfanilamide, preliminary basic hydrolysis was necessary before diazotization; the procedure is noted below. Filtrates of intestinal fluid represented 1:10 and 1:20 dilutions, and of blood, 1:5. Standards for colorimetric comparison were prepared from the fresh solutions used in each experiment.

Recoveries of sulfonamides added to saline washings of cat intestine obtained after a preliminary washing out of fecal material averaged better than 98%. On following the exact technique of the experiment except that the mesenteric vessels were clamped and the intestinal loop removed and opened immediately after the injection, recovery of sulfapyridine was 98.25% and recovery of fluid was 98.75%; there was no sulfapyridine in the blood. The rapidity of absorption of sulfapyridine was

emphasized in a second experiment in which 2 minutes passed between the time of injection and removal of the intestine. Only 85.6% of the agent and 96.7% of the fluid were recovered. A trace of sulfapyridine was present in the blood. Again with sulfapyridine, a 40 minute absorption period was allowed in one cat, with absorption of 98.9% of the agent and 85.7% of the fluid, and a blood content of 1.09 mg. %. In 2 other cats, a 30 minute period of absorption was allowed. In one, 96.6% of sulfapyridine and 75% of fluid was absorbed; in the other, which was exposed to a degree of anoxia approximately equivalent to an altitude of 28,000 ft., 94.7% of sulfapyridine and 47.5% of fluid was absorbed. The content in the blood was 0.93 and 0.91 mg. %, resp. None of these values is included in Table I since the results tabulated were all obtained with a standard absorption period of 25 minutes.

Estimation of 4-Nicotinylsulfanilamide

In the present work, it was found that the ordinary procedure of acid hydrolysis suitable for most conjugated sulfonamides was not applicable to nicotinylsulfanilamide, but that this agent was almost completely hydrolyzed when heated in strongly basic solution. The pH of the mixture was not accurately controlled inasmuch as tests showed that considerable latitude could be allowed without affecting accuracy greatly. For most of the hydrolyses, a pellet of reagent grade KOH was added to each tube.

One of us (J. K. F.) had made this observation while at the University of California, independently of the other, and proceeded to develop a precise controlled method of hydrolysis. This technique is briefly noted here for its possible value in the estimation of other sulfonamides resistant to acid hydrolysis.

One volume of blood is added with shaking to nine volumes of 95% ethyl alcohol. After standing for ten minutes the mixture is filtered in a loosely covered funnel. From one to five ml. of this filtrate is pipetted into a 17x150 mm. test tube graduated to contain 10 ml. of liquid in addition to two small glass beads which are added to prevent bumping during boiling. One ml. of 2N NaOH (or a pellet of reagent grade KOH) is added and the contents diluted to about 6 ml. with distilled water. After being boiled in a water bath for ninety minutes, the contents of the tubes are neutralized to a phenolphthalein end-point with 1N HCl; the volume in each tube is then brought to the 10 ml. mark by the addition of distilled water.

In order that the diazo-reaction will proceed to completion, the reagents used must be cold. The tubes are cooled in cracked ice, and when thoroughly

chilled, 1 ml. of cold, freshly prepared 0.1% sodium nitrite solution is added to each tube with agitation. After exactly 3 minutes, 5 ml. of a solution of dimethyl-alpha-naphthylamine (1 ml. diluted to 250 ml. with 95% ethyl alcohol) is added with shaking. Color development proceeds to a maximum quite rapidly, and the intensity of color may be compared with those of suitable, similarly prepared standards in 5 to 10 minutes. When a photo-electric colorimeter is used, a dark-green (Cenco No. 165) filter is helpful in limiting the color of the light source to nearly monochromatic light thereby increasing the sensitivity of the readings.

Results

Table I presents comparative data on absorption of the 5 sulfonamides and the Na salt of sulfapyridine. In each case, fluid recovered from the intestine is more dilute in regard to sulfonamide content than the fluid administered; a larger fraction of the sulfonamide is absorbed than of the saline. Absorption of fluid itself is not affected by the presence of the sulfonamides. The extremely rapid absorption of sulfonamides is most marked for sulfapyridine and its Na salt, but all the sulfonamides studied disappear rapidly from the small intestine.

Variations in the rate of absorption of different sulfonamides are not correlated with molecular weight, for there is no significant difference between the rates of absorption of sulfanilamide, sulfathiazole, sulfamethylthiazole and nicotinylsulfanilamide while there is a significant difference between sulfanilamide or sulfathiazole and sulfapyridine. Further, with rodilone, a sulfone, the apparent disappearance of 96.7 and 97.2% of the agent in 25 minutes from the intestine of 2 cats given a 0.04% suspension of this relatively insoluble agent would indicate rapid absorption of this heavy acetylated compound. However, the assay method for this agent is not as reliable as for the sulfonamides studied, since the product produced by acid hydrolysis for one hour yields a deep purple dye of limited solubility, on coupling with dimethyl-a-naphthylamine.

Route of Absorption

The rapid rate of absorption of the sulfonamides suggests that these substances might be absorbed to a considerable extent by other routes than through capillaries of the intestinal wall. To test this possibility, the thoracic duct was cannulated

TABLE I

Intestinal Absorption of Certain Sulfonamides in Cats

Agent	No. of Cats	Body Wt., gm.	Fluid Absorbed, Per Cent	Agent Absorbed, Per Cent	Conc. in Gut, mg. Per Cent	Dose Inj., mg./kg.	Dose Absorbed, mg./kg.
Sulfanilamide	10	2242±195	35.5±2.8	75.5±2.3	15.13±1.07	8.35±0.51	6.34±0.50
Sulfapyridine	10	2142±207	55.4±4.3	92.5±1.5	6.33±0.88	8.22±0.48	7.64±0.51
Na sulfapyridine	5	2370±278	50.8±7.7	90.2±1.7	7.47±0.48	8.22±0.13	7.40±0.13
Nicotinylsulfanilamide	5	1440±270	39.4±4.9	63.1±4.1	24.40±2.00	8.25±0.06	5.20±0.34
Sulfathiazole	5	2099±463	39.1±5.2	75.0±4.9	15.72±2.43	8.60±0.22	6.44±0.51
Sulfamethylthiazole	5	2436±476	41.9±8.3	75.0±6.2	15.90±2.49	8.32±0.05	6.20±0.52

in 4 dogs, weighing 12–16 kg., which had been fasted 24 hours, and up to 500 ml. of 0.04% sulfapyridine were injected intraduodenally. Lymph was collected for 4 consecutive 15-minute periods after injection of sulfapyridine. Blood was drawn from the femoral vein at the mid-point of each 15-minute interval. The sulfapyridine content of trichloroacetic acid filtrates of blood and lymph were estimated by the method used above.

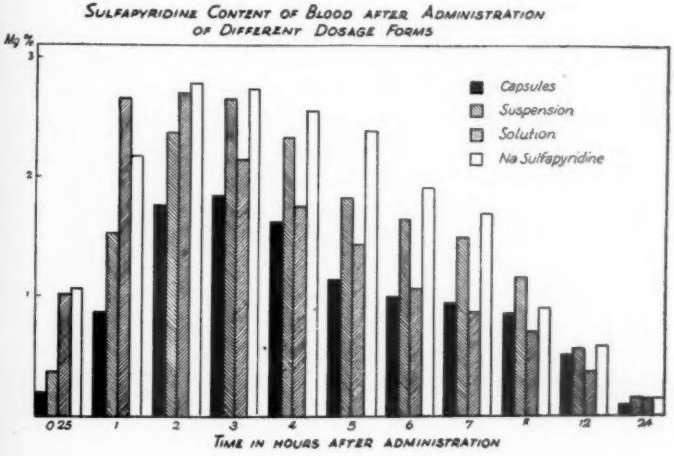
It may be concluded that sulfapyridine is not a lymphagogue, since a flow of 6 ml. in 15 minutes was obtained in only 2 of the 4 dogs; and also that no important fraction of the sulfapyridine enters the circulation through the thoracic duct, since the maximum concentration in the lymph was at best only 50% greater than the apparent concentration in the venous blood taken at the same time. With a low blood content of about 1 mg. %, the apparent concentration of sulfapyridine in blood is much lower than the true value, due to binding of this agent by blood proteins, while sulfapyridine is recovered almost quantitatively from lymph. Thus, there is no real difference between the concentrations found in blood and lymph, and since the lymph flow is not stimulated to a significant degree, lymphatic absorption is not an important route with sulfapyridine.

Dosage Forms

The finding that sulfapyridine is the most rapidly absorbed of the 5 sulfonamides studied is in apparent conflict with clinical experience that "sulfapyridine is irregularly and often poorly absorbed" as stated in *New and Nonofficial Remedies*. The explanation lies in the use of solutions of sulfapyridine in the present work, while solid dosage forms are commonly used clinically. That is, poor absorption of sulfapyridine under clinical conditions is due to the low solubility of this agent rather than to lack of permeability of the intestinal wall to this agent in solution. It has been suggested by several workers that sulfapyridine must be very rapidly absorbed from solution since it is so little soluble. Stead and Kunkel have used the more soluble sulfanilamide as an index of the blood flow in the intestine of man, by intraduodenal administration of 300 ml. of 1% solution.

To test this interpretation of the present results, fasted dogs were given 50 mg./kg. of sulfapyridine by mouth, in the form of capsules, 0.04% suspension, 0.04% solution, and capsules of the Na salt. Dogs were given these 4 dosage forms with an interval of 1 week between each of them, so that each dog received all forms; the sequence in which the different forms were given was different for each dog. Vomiting sometimes occurred after intragastric injection of the requisite large volumes of solution or suspension; the vomitus was returned to the stomach and was retained thereafter. Capsules of free sulfapyridine or of its Na salt were punctured before administration and a small amount of water was given immediately to aid passage of the agent into the duodenum.

Results of estimations of blood content at intervals after administration of the different dosage forms were averaged for each form, and are presented in Figure 1. The values given



refer to the concentrations of sulfapyridine actually found in trichloroacetic acid filtrates of blood and are uncorrected for sulfapyridine bound by the blood. It may be noted that the absorption of sulfapyridine was slow and incomplete after ingestion of the solid agent in capsules; most rapid after administration of the 0.04% solution; and nearly as rapid and considerably more sustained after treatment with either the 0.04% suspension or capsules of the Na salt. The simultaneous

administration of large amounts of fluid and of $NaHCO_3$ should be useful in making the absorption of sulfapyridine more rapid and uniform.

Acknowledgment

The larger part of these studies was completed in 1939–1940 with the expectation of extending them, as opportunity permitted, by a comparison of absorption under anoxic conditions in cats. We are grateful for the interest and encouragement of Dr. E. J. Van Liere and his colleagues in the Department of Physiology of West Virginia University School of Medicine.

Summary

Intestinal permeability to 0.04% solutions of 5 sulfonamides and the Na salt of sulfapyridine was studied by the technique of Van Liere. All the sulfonamides tested were absorbed very rapidly, more rapidly than the 0.9% NaCl used as a solvent. Sulfapyridine was absorbed most rapidly, nicotinylsulfanilamide most slowly; sulfanilamide, sulfathiazole and sulfamethylthiazole were intermediate between these two. Na sulfapyridine was absorbed from solution at essentially the same rate as sulfapyridine. No appreciable fraction is absorbed through the lymphatics of the intestine. The rapid absorption of sulfapyridine from solution is contrasted with the slow and irregular absorption of solid sulfapyridine given in capsules, and the sulfapyridine content of blood of dogs was followed at intervals for 24 hours after oral administration of this agent as capsules, 0.04% suspension, 0.04% solution, and capsules of the Na salt.

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EFFECT OF ANOXIA ON INTESTINAL ABSORPTION OF SULFAPYRIDINE IN CATS

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Sulfonamides are frequently used in patients exhibiting moderately severe anoxia. It has been shown (Emerson et al., 1940) that none of 3 sulfonamides given parenterally affects the susceptibility of experimental animals to lethal effects of anoxic anoxia. On the other hand, it is noted by Mackie and Rook that sulfanilamide lowers the "ceiling" for aviators and that disorientation and diminished precision of judgment are caused by sulfonamides, so that, in practice, flying should be proscribed for aviation personnel after sulfonamides have been administered.

It is of interest to study quantitatively the variations of intestinal absorption of sulfonamides in anoxic animals, for the maintenance of an effective blood level of the sulfonamides depends on the rate of absorption as well as on the dose given. Variations in the physiological process of absorption in pneumonia or other conditions accompanied by anoxia are therefore important from the therapeutic viewpoint.

METHODS

Methods employed are similar to those in the preceding study (Emerson and Finnegan). Twenty adult cats were divided in pairs matched in weight. Each pair was starved 24–36 hours and given 220 mg./kg. Na barbital intravenously. A 40-inch loop of small intestine was ligated at each end after washing the lumen with saline at 40°; a freshly prepared, warm 0.04% sulfapyridine solution was then injected until the intestine was moderately distended. The volume required was usually about 20 ml./kg. and was accurately measured. After closure of the abdomen, one of each pair of cats was subjected to anoxia in a decompression chamber resembling that of Kolls and Loevenhart. The other cat was kept on top

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of the decompression chamber, under room conditions but subjected to the same slight stimuli of noise and vibration as the anoxic cat. The loop of intestine was removed 25 minutes after the injection, opened longitudinally and stripped to collect all fluid in its lumen. The fluid recovered was measured to 0.25 ml. Blood was obtained intracardially. Chemical techniques for estimation of sulfapyridine content of blood and the recovered fluid are described in the preceding study.

Results

Results obtained are noted in Table I. Little effect of anoxia is apparent even in cats subjected to 254 mm. Hg pressure, which corresponds to an altitude of approximately 28,000 ft. At the higher level of 382 mm. Hg pressure (18,000 ft.), the effect is still less. Results are expressed in several ways: the average dose injected and the average dose recovered; the average per cent absorption of sulfapyridine; and the concentration of sulfapyridine in the fluid remaining in the intestine after the absorption period. In the first, the variations in dose necessary to ensure a uniform physiological preparation, with approximately the same amount of distention of the intestine in all cats, obscure the small changes induced by anoxia. The second yields a more precise measure of the small changes since it is calculated as the mean of the per cent absorption in individual cats. The third measure must be considered in relation to the amount of fluid absorbed. Thus, the average per cent absorption of sulfapyridine affords the most accurate measure of the effect of anoxia.

It may be noted that anoxia of the degree present at a simulated altitude of 28,000 ft. causes a statistically significant reduction in the absorption of sulfapyridine and of fluid. The odds (p) that these differences are due solely to chance are less than 1:200. However, the difference in absorption of sulfapyridine is so small that it has no clinical significance. There was no significant difference in the sulfapyridine content of blood in anoxic and control cats, at either level of anoxia.

TABLE I

Intestinal Absorption of Sulfapyridine in Cats Subjected to Anoxia

	No. of Cats	Average Body Wt., gm.	Dose Injd., mg./kg.	Dose Absd., mg./kg.	Per Cent Sulfapyr. Absorbed	Per Cent Fluid Absorbed	Conc. in Intestine, mg., Per Cent
Experiments at 254 mm. Hg Pressure							
Controls	5	2024	8.32±0.73	7.90±0.79	94.6±1.39	58.4±4.6	4.98±0.90
Anoxic	5	2014	8.37±0.82	7.37±0.85	87.3±1.82	38.3±4.2	7.97±0.80
Difference	....	10	0.05	0.53	7.3±2.26	20.1±6.3	2.99±1.21
Experiments at 328 mm. Hg Pressure							
Controls	5	2260	8.12±0.69	7.39±0.72	90.7±2.40	52.4±7.5	7.68±1.03
Anoxic	5	2326	7.88±0.70	6.69±0.74	84.5±3.90	38.1±6.5	9.38±1.64
Difference	—	76	0.24	0.70	6.2±4.60	14.3±9.9	1.70±1.93

Sulfapyridine is more rapidly absorbed than the fluid in which it is dissolved. The consequent dilution of the intestinal fluid as regards sulfapyridine is not appreciably affected by severe anoxia.

Comparison of the effects of anoxic anoxia on the rates of absorption of fluid from solutions of 0.9% sodium chloride and of 0.9% sodium chloride containing 0.04% sulfapyridine is of interest. Van Liere and Sleeth found that exposure to a level of anoxia representing an altitude of 18,000 ft. reduced absorption of saline over a 40-minute period to about 85% of that of control animals; however, they found that at an approximate altitude of 28,000 ft., the absorption of fluid was about 90% that of the controls. With saline containing sulfapyridine, the present work shows absorption of fluid only to the extent of about 75% as much as in the controls, at the more moderate level of anoxia; and about 65% as much as in controls, at a simulated altitude of about 28,000 ft. These findings suggest that sulfapyridine may have some influence on the effects of anoxia on fluid absorption from isotonic saline.

Interpretation of Results

Absorption of drugs by the patient after peroral administration depends upon many factors other than those influencing permeability in the intestinal tract; e.g., solubility of the drug within the pH range encountered in the stomach and small intestine, resistance to the action of digestive ferments, influence of fats or other foodstuffs on the drug, effect of the drug on stomach emptying time, emetic effects of the drug, and effects upon intestinal motility. Van Liere, Lough, and Sleeth have shown a progressively increasing retardation of stomach emptying with degrees of anoxia exceeding that at a simulated altitude of 8,000 ft. Effective propulsive motility of the small intestine is less sensitive to anoxia, but a decrease is noted (Van Liere et al., 1943) under certain conditions at moderate degrees of anoxia. Thus, in the anoxic patient, absorption of sulfapyridine may be decreased by other factors even though there is no change in the permeability of the intestine to this substance.

ACKNOWLEDGMENT

Thanks are due Dean E. J. Van Liere for permitting use of a decompression chamber in the Department of Physiology of West Virginia University School of Medicine and for his encouragement in the prosecution of this study.

SUMMARY

Effects of anoxic anoxia on intestinal absorption of sulfapyridine in cats were studied. The extremely rapid rate of absorption of sulfapyridine from saline solution is decreased only slightly at levels of anoxia corresponding to altitudes of 18,000 and 28,000 ft. The small decrease is statistically significant with the more severe degree of anoxia, but there is no important difference in sulfapyridine content of blood after the absorption period, even at this level. From the clinical viewpoint, moderately severe anoxia has no appreciable effect on permeability of the small intestine to sulfapyridine.

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EFFECTS OF NEOSYNEPHRINE AND PRIVINE ON CELLS *IN VITRO*

CHARLES M. POMERAT, MADELINE LAY, AND G. A. EMERSON*

Among the numerous preparations applied to the nasal mucosa to give symptomatic relief in the common cold, neosynephrine and privine solutions are two of the most generally used. Neosynephrine is a sympathomimetic amine with properties characteristic of this group and is suited for nasal use by its high potency as a vasoconstrictor, relatively long duration of action and freedom from irritant effects. Its vascular actions are partly adrenergic and partly direct; its pressor effect is decreased but not reversed by sympatholytic agents. Privine (2-naphthyl-1′-methylimidazoline HCl) is a new agent totally unrelated in any chemical way to the sympathomimetic amines. Its vascular actions are mainly direct, with a somewhat smaller portion than with neosynephrine mediated through adrenergic mechanisms. Few substances not having the typical structure of the pressor amines are appreciably stimulant to vascular muscle, but Meier and Müller have shown privine to be among the most potent vasoconstrictors when applied locally to the mucous membranes. Cardiovascular effects following parenteral administration have recently been studied by one of us (Emerson). Crystalline privine HCl was generously supplied by the Ciba Pharmaceutical Company, Inc., of Summit, N.J.

Neosynephrine is well tolerated systemically as well as locally, while privine has grave toxic effects upon the heart in doses only slightly larger than those producing moderate pressor responses. Yonkman *et al.* have demonstrated that there is very poor absorption of privine from mucous membranes of the dog, and Fabricant and Van Alyea noted no systemic reactions in man even after instillation of this agent into the maxillary sinus. Under ordinary circumstances, ab-

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sorption of toxic amounts of privine from the nasal mucosa is not likely to occur.

It remains to compare local effects of privine upon tissues with those of neosynephrine, as a representative pressor amine. Fabricant and Van Alyea state that privine solutions are not detrimental to ciliary activity, basing this conclusion apparently on the pH of secretions following its use. Excessive drying of the nasal mucous membrane following application of privine may occur, however, and interference with normal physiologic processes might result. Epinephrine is known to produce undesirable effects locally after subcutaneous injection, through prolonged ischemia (Hrubetz). Another approach to the problem is reported here. Studies of effects of these agents upon growth of cells in tissue culture yield a measure of direct effects on essential physiologic processes in tissues, independent of effects on circulation or water balance of the cells.

Materials and Methods

The object of these experiments was primarily to compare the minimal toxic dose of neosynephrine with that of privine. The method used was one which had been effectively employed by Medewar (c.f., Abraham *et al.*, 1941) which consists of determining the concentration of the drug just sufficient to prevent the outgrowth of cells from freshly explanted embryonic fragments. Secondly, effects on growth with concentrations likely to be attained in the cell environment under the conditions of clinical use were more intensively studied by the same technique.

Seven to ten day embryos were used as source material for (1) heart fibroblasts, (2) intestinal epithelium, and (3) lung epithelium. All tests were conducted in hanging drop preparations in a medium made up of 12 per cent embryo extract and rooster plasma. Neosynephrine HCl and privine HCl solutions were incorporated in the embryonic extract at appropriate concentrations after having been passed through a Swinny micro-Seitz filter which insured their sterility.

Experiment 1

In this series the response of chick heart fibroblasts was tested against concentrations of both neosynephrine and privine at 1–50,000; 1–10,000; 1–5,000; and 1–1,000. Four hanging drop preparations were made for each of these eight tests in addition to eight untreated controls. After 48 hours incubation at 37.5° growth comparable with that of the controls was found at concentrations up to 1–5,000 for neosynephrine while at 1–1,000 only a few cells had migrated from the explants and these showed marked vacuolation and irregularities of form typical of an injury reaction. Privine did not damage fibroblasts at concentrations as high as 1–10,000 but at 1–5,000 a poor outgrowth was produced of "stringy" and markedly vacuolated cells. Absolutely no growth occurred at 1–1,000.

Experiment 2

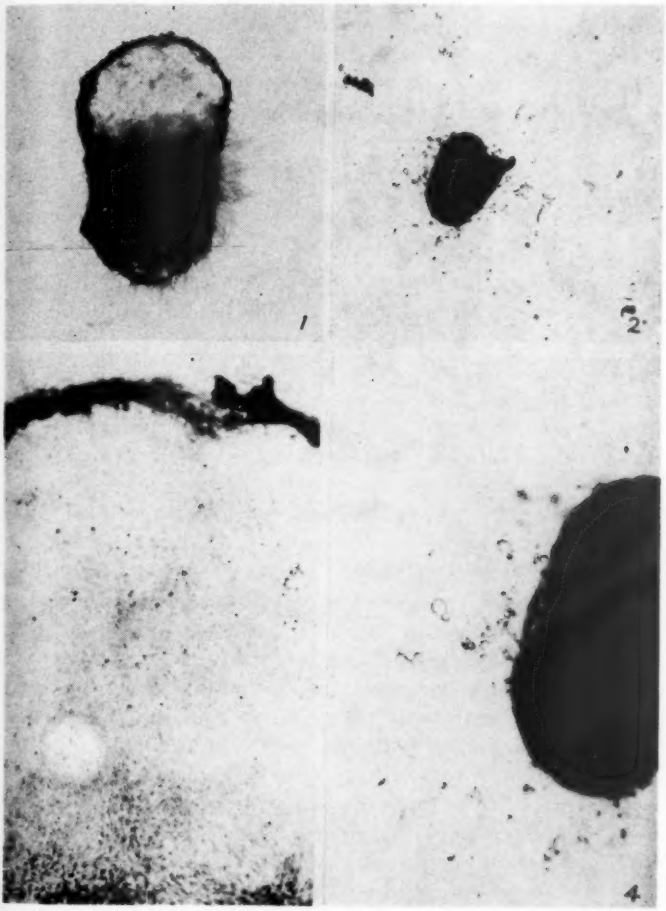
Using the same technique as in the first experiment, tests were repeated to determine the minimum inhibitory dosage more precisely and to extend the observations to epithelium. Sections of the intestine are particularly adapted for the study of epithelial growth due to the facility of handling cultures.

Neosynephrine. Migration of fibroblasts equivalent to those of the controls was found at concentrations of 1–5,000; 1–4,000; 1–3,000, and 1–2,000; but at 1–1,000 outgrowth was considerably reduced. Similar results were obtained for epithelium except that relatively good outgrowth occurred at 1–2,000 with almost complete inhibition at 1–1,000. Typical results as seen in stained preparations of epithelium are represented in Figures 1 to 4.

Privine. Experiments with privine were conducted at 1–10,000; 1–9,000; 1–8,000; 1–7,000; 1–6,000, and 1–5,000. Normal cellular outgrowth of both fibroblasts and epithelial cells occurred at all of these concentrations. It was, therefore, found necessary to repeat the experiment at concentrations of less than 1–5,000.

Experiment 3

Neosynephrine. Inhibition of outgrowth for both fibroblasts and epithelium at 1–1,000 and good growth of fibroblasts at



Figs. 1–4. Hanging drop cultures of intestinal epithelium. In Figures 1 and 3 the explant was grown in neosynephrine 1–5000, while in Figures 2 and 4 a concentration of 1–1000 was used. Figures 1 and 2 at 55 diameters. Figures 3 and 4 represent details of corresponding outgrowth at 425 diameters. The size of the original explant (dense black mass) was approximately the same in both cultures.

1–2,000, 1–3,000, 1–4,000, and 1–5,000 was confirmed. In subculture very slight recovery was found for tissue previously exposed for 84 hours to neosynephrine at 1–1,000.

Privine. Outgrowth resembling that of the controls was normal for both heart and intestinal explants at concentrations of 1–7,000, 1–6,000, and 1–5,000, while total inhibition was found at 1–4,000 and 1–3,000. Very few cells migrated from subcultures of explants exposed to 1–4,000 privine.

Experiment 4

The object of this experiment was to determine the effect of neosynephrine and privine on fibroblasts and epithelium derived from embryonic lung at concentrations within the range of therapeutic usage, taking into consideration dilution by mucous secretion and the factor of the persistence of these drugs on tissue surfaces. Concentrations of both drugs for tests on heart and lung explants were prepared at 1–5,000 and 1–10,000 for neosynephrine and for privine. Eight hanging drop preparations were made for the ten conditions including untreated controls.

Using a projectoscope, outlines of colonies were projected on graph paper at a magnification of 11 diameters. The relative areas of the outgrowth at initial, 36, 60, and 84 hours is represented in Figure 5. Since fragments of various sizes are known to reach roughly the same ultimate area of outgrowth in untreated preparations, the data have been plotted in terms of per cent outgrowth from the size of the original explant.

Results show that both drugs at 1–5,000 permitted less cellular migration from explants than the controls but that at 1–10,000 both stimulated outgrowths beyond those obtained for corresponding controls with the exception of privine 1–10,000 in heart cultures. The possible importance of this finding especially with respect to epithelium suggested the need of confirmation.

Experiment 5

Twenty cultures were set up for untreated, neosynephrine at 1–10,000, and privine at 1–10,000, in parallel for both lung and intestinal explants. Projection outlines of colonies were

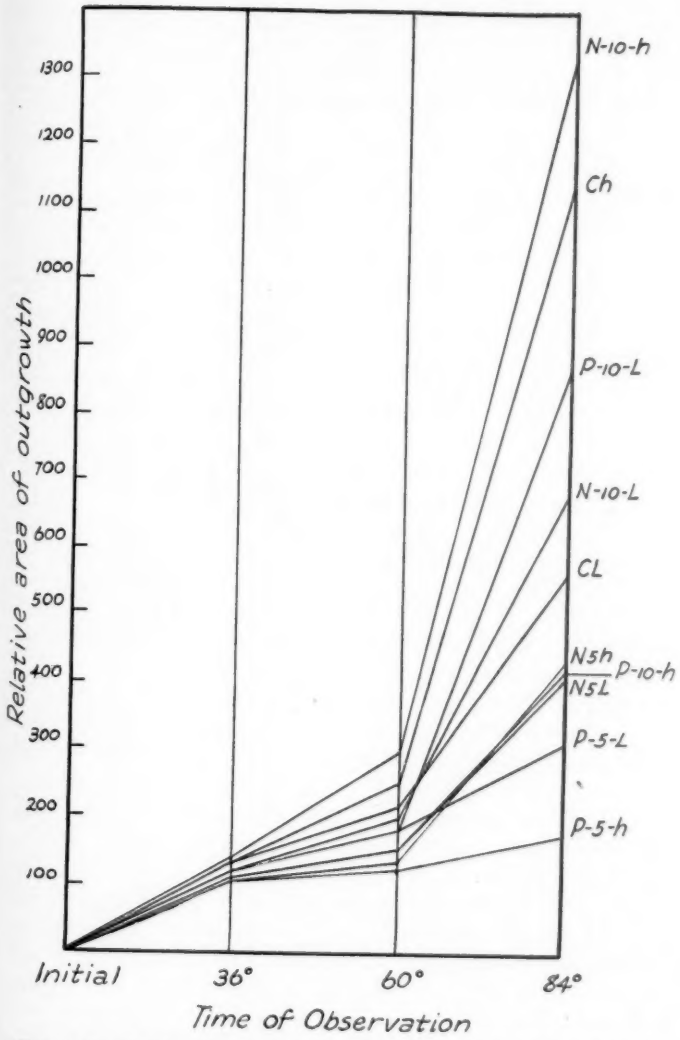


Fig. 5. Relative increase in area of heart (h) and lung (L) explants in medium containing Neosynephrine (N) at 1–10,000 (10) and 1–5,000 (5), and Privine (P) at similar concentrations in comparison to untreated controls (C). Experiment IV.

made at initial, 15, 39, 63, and 87 hours. Comparison of the per cent final outgrowth in each of the six conditions is given in Table I which shows no significant stimulus for epithelial growth by either neosynephrine or privine at this concentration.

TABLE I

Comparison of percentage outgrowth of epithelial cells in vitro *in relation to neosynephrine and privine. Twenty cultures were measured for each condition*

	Lung		Intestine	
	Mean	S.E.	Mean	S.E.
Control	189	27	449	60
Neosynephrine 1–10,000	238	34	410	41
Privine 1–10,000	223	30	276	52

DISCUSSION

Neosynephrine HCl is supplied commercially in 0.25 and 1.0 per cent isotonic saline solutions, 0.25 per cent Ringer's solution and 0.5 per cent jelly. The 0.25 per cent solutions are sufficiently potent to relieve most instances of nasal congestion. Privine HCl is supplied in 0.1 per cent buffered isotonic aqueous solution for adults and 0.05 per cent for children. Both solutions are powerful decongestants.

It may be noted that, in use, privine is generally applied in 0.4 the concentration of neosynephrine, whereas the inhibiting effect of neosynephrine on fibroblasts and epithelia is but 0.25 that of privine.

These considerations must be interpreted with due regard for the difference in conditions *in vitro* and in clinical use. In the former, the explant is in contact with a relatively great excess of the agents and the time of contact before observations can be made is necessarily long. In the latter, the agents are applied in relatively small amounts to edematous tissues well protected by mucus, and the time of contact is shorter. Factors of permeability therefore are of much more importance with intact tissues than with explants. Neosynephrine is absorbed in quantity from mucous membranes such as that of the intestine far more readily than is privine. On the other hand, the

prompt local vasoconstriction caused by privine demonstrates that an appreciable amount of this agent rapidly penetrates the epithelium to produce its vascular effect, and suggests that this vasoconstriction is the limiting factor in determining absorption, rather than poor permeability. However, even though both privine and neosynephrine are supplied for clinical use in concentrations exceeding those toxic to fibroblasts and epithelia in tissue culture, it is improbable that the nasal tissues are exposed to toxic concentrations for a sufficiently long period to produce any irreversible changes. After exposure for as long as 84 hours to 0.1 per cent neosynephrine or 0.025 per cent privine, fibroblasts and epithelia still showed some recovery on subculturing.

Morphologic alterations in growing cells exposed to concentrations of the two agents within their toxic ranges are of interest in view of the studies of Lettré and Albrecht. These workers describe formation of aqueous vacuoles in fibroblasts from chick heart explants exposed to various amines. They report that NH_3, NH_4Cl, a number of aliphatic amines, benzylamine, phenethylamine, ephedrine, suprifen (*p*-hydroxyephedrine), hordenine, mescaline, tyramine, synephrine, paredinol, and also histamine all share this property, while various quaternary ammonium compounds and weak nitrogenous bases including choline, acetylcholine, thiamine, the three aminobenzoic acids, tyrosine, and dihydroxyphenylalanine do not. To the list of nitrogen compounds causing vacuolation of fibroblasts may be added neosynephrine and privine.

Acknowledgment

We are grateful to Miss Betty Jones for technical assistance in this work, and to Dr. J. A. Scott for his interest and help.

Summary and Conclusions

In vitro experiments using explants of heart, intestine and lung show that fibroblasts and epithelia are not inhibited differentially. Inhibition is effected at a concentration between

1–1,000 and 1–2,000 by neosynephrine and between 1–4,000 and 1–5,000 by privine. At dosages used in clinical practice these drugs are not inhibitory.

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A RAPID CURE FOR INFANTILE VISCERAL LEISHMANIASIS BY A NEW FRENCH ANTIMONIAL DERIVATIVE*

J. Sarrouy, R. Dendale, P. Combe, R. Arnaud, and F. Gillot†

Since the summer of 1940 we have had the opportunity of experimenting upon eight different children suffering from visceral leishmaniasis with a new derivative of pentavalent antimony discovered by Professor L. Launroy of the University of Paris in 1937.

The drug is the amino-phenyl-stibinate of methyl-glucamine, made available by the French firm "Specia" under the name of "Pentastib," which was first used only in veterinary therapy. Two of our cases were reported to the Medical Society of Algiers as early as February, 1941 (1). Results on the others have not yet been published. To our own knowledge the only reports about a method similar to our own are those by Coulon (2) in a study of a girl of 3½ years, and those by Garin, Coudert, and Guinet (3) upon an adult. Wartime difficulties account for our omission of these results in our preliminary publication.

Clinical Observations

Our observations have been published in full in Miss Boniface's thesis (Infant Clinic of the University of Algiers). All our observations concern children from the environs of Algiers presenting the clinical symptoms of Kala-Azar: irregular temperature often lasting for months, hepato- and splenomegaly, micropoly-adenopathy; anemia, leukopenia with inversion of the leucocytic balance. In all these cases, diagnosis was confirmed by the presence of Leishmann bodies in smears of spleen or bone marrow. In all of these patients characteristic

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disturbances of the blood albuminoids were also found. The following is a record showing the results obtained according to the posology and the timing of injections employed in these different observations. We have classified our cases in three groups:

Group A: rapid recovery.
Group B: a slower recovery.
Group C: a very slow recovery.

(1) Efficiency of the Treatment

In the 8 cases summarized in our table, clinical and hematological recovery was obtained. Full efficiency of the new derivative was demonstrated but we should like to point out differences in the rate of recovery in these cases.

Group A (Cases 1, 2, 3, 5)

The duration of the treatment did not exceed six days and sometimes before the last day the temperature came back to normal. The general condition of these patients changed in a few days: immediate return of appetite, increase in weight and of liveliness.

Hematological recovery is slower in manifesting itself. The red cell number and leucocytic balance comes back to normal

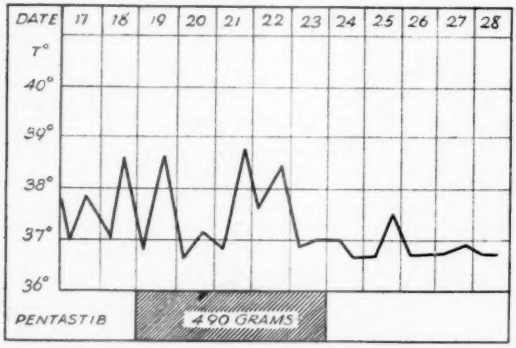

Fig. 1 Case No. 1 Charlotte G..... 5 yrs.

TABLE I

Summary of Cases Studied

Case Number	Name	Results	Age	Weight in Kilograms	Dose in Grams	Number of Days Treatment Was Given	Average Dose Per Kilogram	Average Dose Per Kilogram and Per Day
1	Charlotte	A	5 yr.	12.8	4.20	5	0.38 g.	0.0766 g.
2	Bachir	A	4 yr.	12.3	5.25	6	0.42	0.0711
3	Charles	A	3 yr.	12.0	3.25	4	0.27	0.0677
4	Rosalie	B	6 yr.	15.6	4.75	10	0.30	0.0304
5	Armande	A	4 yr.	12.0	2.50	3	0.209	0.0699
6	Georges	C	9 mo.	6.5	8.25	155	1.27	0.0082
7	Kafir	B	11 mo.	7.7	4.00	12	0.51	0.0444
8	Robert	B	3½ yr.	13.15	5.25	24	0.39	0.0169

in about one month. In the same way the disturbances in the albuminoids of the blood persisted 2 or 3 months, forming a kind of serological cicatrix (Cases 1 and 2). Hepatomegaly and splenomegaly decrease slowly in a period varying according to our cases. Liver and spleen will return to their proper form only between 1 and 3 months after the end of treatment.

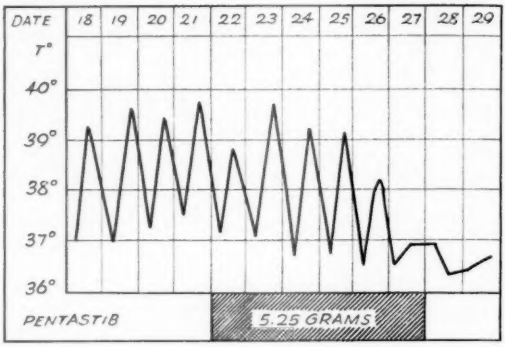

Fig. 2. Case No. 2. Bachir S. . . . . 4 yrs.

Group B (Cases 4, 7, 8)

These showed that treatment during a time double or quadruple that of the preceding observations (10, 12, and 24 days instead of the 5, 6, 4, and 3 days) gives favorable results also, but not as rapidly.

In Case 4 the temperature came back to a normal level only 4 days after the end of the treatment, though absence of Leishmann bodies was established in the shinbone marrow just after the third day of the treatment.

In Case 7 an abscess in the buttock obliged us to interrupt the treatment.

Case 8 may be usefully compared to Case 2 since these were children of the same weight having received the same total dose of "Pentastib." Only the duration of the treatment differed. In the two cases recovery was obtained, but much more effectively and rapidly in Case 2 (6 days of treatment) than in Case 8 (24 days of treatment).

Comparison of the two fever charts established the greater efficiency of the shorter treatment (immediate drop of the temperature in Case 2, persistence of some thermal fits in the evenings during a week after the end of the treatment in Case 8).

Group C (Case 3)

This case shows that light doses of the drug (0.25 or 0.50 gms. daily) during short treatments separated by long intervals gives bad results. Final recovery could only be obtained after 155 days of treatment and a total dose of "Pentastib" far greater than that employed in the other cases.

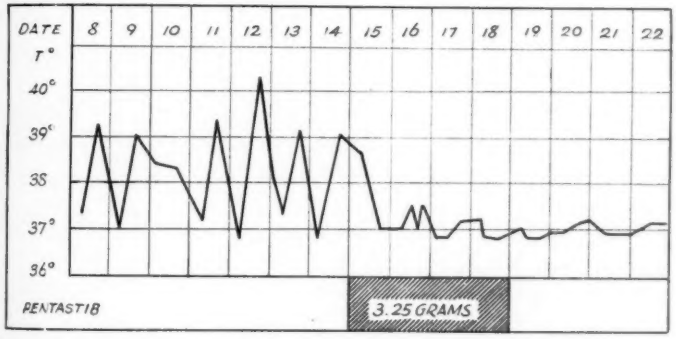

Fig. 3. Case No. 3. Charles F. . . . . 21½ yrs.

A comparison of our observations with those of Coulon (2), and Garin, Coudert, and Guinet (3) is very instructive. Coulon injected a little girl of 3½ years, weighing 12.9 K., with 19.75 grams of "Pentastib" in 35 days. Garin, Coudert, and Guinet gave an adult (21 years of age) 85.50 grams in two months, after failure with "New-Stilbosen" and of "Diamidine" (a new British anti-Leishmann drug without antimony). These authors became convinced, independently, of the value of a single strong dose. We believe that such quantities, relatively much greater than ours on a basis of weight, could have been diminished if the injection had been reduced to a shorter time.

The study of these observations and of our charts leads us to the conclusion that the best results were obtained when the total doses of the medicine had been injected during the shortest time; i.e., when the average dose per kilogram and per day is highest (Cases 1, 2, 3, 5). What matters is not the injection of an average dose per kilogram (for instance in Case 6: 1.27 gms.) but to strike quickly.

(2) The Ill Effects of the Treatment

The treatment with large doses given frequently over a short period may seem dangerous. In reality the inocuity of this drug has been checked for the liver and kidney parenchyma by functional tests (provoked galactosuria, elimination of phenol-sulfonphthalein in the urine, urinary densimetry) in many of our cases and the treatment was never found to provoke any complication. Moreover, in Case 2, we were concerned with a child, sick for a year, in a cachectic state, with an 18 cm. spleen and a 10 cm. liver along with symptoms of portal hypertension (venous collateral circulation, Rivalta test positive ascitic but without Leishmann bodies). Recovery was complete and without incident.

Complications in Case 4 might have made one timid (light albuminuria, some red cells and some granular cylinders in urine, retarded elimination of the P.S.P.), but the child tol-

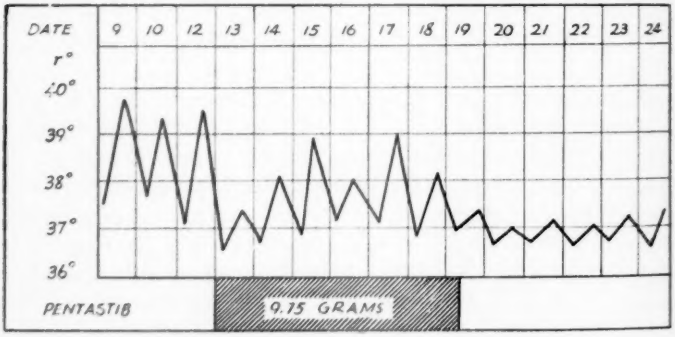

Fig. 4 Case No 9 Robert M..... 10 yrs

erated the treatment perfectly and urine examinations ultimately showed the disappearance of albumin.

Nevertheless, a few complications during the course of treatment by "Pentastib" should be mentioned.

(a) The most frequent is vomiting or some nausea following the first injection; but, what is most remarkable, is that the other injections have no further effect.

(b) Some abscesses at injection points were noted in Cases 6 and 7 but we should not hold "Pentastib" responsible for these difficulties.

(c) A zosteriform eruption appeared on the 25th day of our Case 2 and in the intercostal zona of Garin, Coudert, and Guinet's patient after his treatment but these can best be explained as mere coincidence.

Remarks from the Pharmacological Point of View

The work of different authors leads us to believe that from the pharmacological point of view the massive and rapid treatment of Kala-Azar by "Pentastib" is logical.

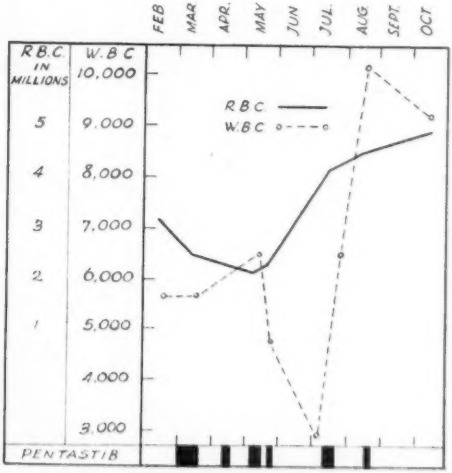

Fig 5 Case No 6. Here the injections were too weak and too far apart (oseries). The blood picture became normal after 5 months treatment

Since 1925, Brahmachari (4) has urged an intensive and short treatment with urea-stibamin. D'Oelnitz (5) recommended the same medicament, used in the same intensive way, followed by hepatotherapy.

From the experimental point of view, Launoy's work (6, 7, 8) and that of Panisset and Grasset (9), are confirmed by the conclusions of Faure-Brae (10) in veterinarian therapeutics.

The elimination of the medicament in urine is great during the first four hours. By the 24th hour following injection more than 50 per cent of the antimony is eliminated. On the other hand, it seems that there is an intra-tissue accumulation of antimonial derivatives, especially in the liver. Finally, we arrive at the idea of "antimonial capacity"; i.e., "quantity of antimony which remains in the organism after a series of stibial injections," a notion clearly demonstrated by Bisquerra (11). This author showed that among the many factors influencing this antimonial capacity the rapid rhythm

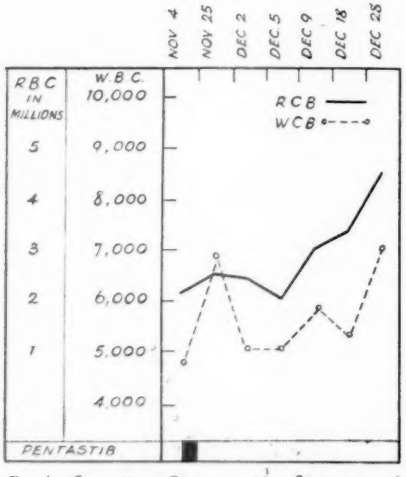

Fig. 6. Case No. 1 One month after a single massive dose of Pentastib. Return to a normal blood picture is almost complete.

of injections and increase of the injected doses are the most important.

Modern knowledge regarding drug resistance in syphilis and trypanosomiasis shows that the institution of a high dosage, given all at once, should be employed. In other words, the use of the maximum dosage which can be safely tolerated.

The chemical resemblance between "Pentastib" and the sulfa drugs should be noted (Harvier and Perrault, 12). 1.162 F. is the para-amino-phenyl-sulfamide and "Pentastib" is a para-amino-phenyl-stibinate. As we know, it is the para position which seems to be important in the activities of sulfa drugs. In both cases, the drug is eliminated in the same way and it is necessary to use strong doses in a very short period.

Conclusions

(1) Para-amino-phenyl-stibinate of methyl-glucamine constitutes a product particularly usable in the cure of infantile visceral leishmaniasis.

(2) The dosage must be as high as possible and injected in a very short period. Here is our actual posology: intramuscular injections of a dose of 0.07 gram per kilogram of body weight per day, during 4 days, regardless of the child's age. These figures constitute an average which we advise, because the medicament's posology has not yet been fixed. But we have had the tendency to increase the amount and to shorten injection time; i.e., 0.10 gram per kilo per day during three days.

(3) The intramuscular route is much the most practical for children. We do not think we should use intravenous injections although the harmlessness of the drug by this method was proved experimentally. The injection of a single and massive dose by slow and uninterrupted venous perfusion may, however, be worthy of trial.

(4) The technique of the injections is the following: First, test the individual's susceptibility following one injection of 0.25 gram, then inject three daily doses so as to spread the absorption of the drug during a period of 24 hours.

(5) Additional associate therapeutic measures such as the injection of hepatic extract (D'Oelnitz) or of cystein and glutathion (Launoy) appears unnecessary.

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MAINTAINING MEDICAL IDEALS

TINSLEY R. HARRISON*

President Rainey, Dean Leake, Members of the Board of Regents, Fellow Physicians and Fellow Students of Medicine:

When almost the entire world is engaged in worship at the altar of Mars we are perhaps justified in wondering what the future may hold for those who prefer to make their offerings at the shrine of Aesculapius. The young physician of today is entering upon his career at a difficult time. His training medical school has been impaired by the absence of some of the ablest and most inspiring of the younger teachers. Acceleration of the curriculum has left him so busy *ingesting* new facts that he has had little time to *digest* them. The chance to learn during the interneship is decidedly diminished and many of the men who are going into the armed forces will find only limited opportunity to obtain either broad or thorough training.

But this is only part of the picture. We must remember that the disorganization of medical education is world-wide and that the degree of disturbance is less in the United States than in any other large country. Some of our recent graduates are receiving excellent training in the Army and Navy hospitals. Apparently there is some compensation for the difficulties and deficiencies of the moment, for we should bear in mind the historical paradox that war—the art of *destroying* human life—has often led to remarkable advances in medicine—the art of *preserving* human life. Thus, the greatest strides taken in surgery during the period of the Renaissance were the outgrowth of the military experience of that remarkable Frenchman, Ambroise Paré. Similarly, the modern understanding of functional disorders of the heart dates from the observations made

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*Graduation address, The University of Texas School of Medicine, June 24, 1944, by the Dean of the Southwestern Medical College, Dallas. From the Departments of Medicine and Experimental Medicine of the Southwestern Medical College. The author apologizes for using extensive quotations from an address made some years ago at the University of Michigan. Such parts of the address have been placed in quotation marks.

by Da Costa during the American Civil War. Likewise, the discovery of the role of the mosquito in the transmission of yellow fever, and the consequent almost complete eradication of this dread disease from North America, was the direct result of the Spanish-American War. Both the first and the second World wars have led to numerous advances in almost every field of medicine. Thus we must admit that out of the past catastrophes of mankind much that is good has emerged and the process is continuing.

Many of you who are today entering the medical brotherhood realize that your education has but begun and that even after you have completed your interneship and served in the armed forces, further training in your chosen field of medical work will be desirable. You are probably interested in knowing what your opportunities will be for such training. In order to attempt to evaluate the situation in the postwar period it is necessary that we have a clear understanding of the conditions prevailing prior to the war.

"The character of instruction offered to undergraduate students was possibly better than had hitherto been available anywhere. The opportunities for training as internes and as residents were slowly improving, although still seriously inadequate. The investigation pursued in many institutions was exceptional in quality and ample in volume. An impartial observer, surveying the rapid progress in neurosurgery, infectious diseases, hematology, endocrinology, cardiovascular disorders, nutrition and metabolism—to mention only a few of the numerous fields of medicine in which important advances were being made—would probably have concluded that the center of gravity of the medical world had shifted from Europe to North America.

"The factors responsible for this remarkable improvement in medical education during the present century are not difficult to find. The dominant one was the introduction of the university principle—or the full-time system—into both the preclinical and the clinical departments of the medical schools. Teaching, which in 1900 was regarded as secondary to the demands of a busy practice, and research, which at that time scarcely existed

in most medical schools, were in 1940 recognized as the chief duties of our faculties. This development was fathered by Abraham Flexner's study of medical education and was nurtured by generous endowments and by judicious appropriations.

"That the full-time *system* itself is valuable is demonstrated by the relatively high quality of instruction offered today in most of the medical schools. Anyone who compares at random a group of a dozen physicians aged thirty, with a similar group twice as old, can scarcely fail to be impressed by the results of the full-time system. But herein lies a danger. Achievement leads to contentment; contentment breeds complacency; complacency induces stagnation; stagnation causes decay. Such is the usual history of cultural organizations and anyone who holds that medical schools possess some particular immunity against this process of institutional arteriosclerosis need only think of Salerno, Montpelier, or even Vienna.

"To say that American medical education is chiefly threatened by that endemic disease—smugness—is to accept the hopeful prognosis. Probably the more serious threat comes from that epidemic disease—barbarism—which even now is destroying the culture of much of the world. At best we face an era of increasing taxation, declining endowments, and diminishing appropriations. It is possible that many good cultural enterprises will be abandoned and that only those institutions which are *superlatively good* will survive. It therefore behooves us to consider means not of making good schools from bad ones, but of making better schools from good ones.

"The importance of the full-time system has been stressed. However, history teaches that in all fields of human endeavor the systems devised by wise men do not function efficiently if they are operated by incompetent persons. The value of a medical school depends on many factors but perhaps the most important of these is its capacity to train leaders in medicine. If the finished product is to be outstanding it is necessary to have the best possible raw material. A competitive system, whereby scholarships carrying a thoroughly adequate stipend would be available to five or ten per cent of each class, would probably attract a larger percentage of unusually gifted

students. If one good school should adopt such a plan—and the others failed to do so—it would soon attract a disproportionately large group of the best young minds, and within a decade or two would probably be the leading institution in the country.

"But it is not enough to try to attract the ablest students. Untiring efforts should be made to improve the personnel of the faculty. More time and thought should be devoted to choosing the instructors and other younger permanent appointees. At present such selections are often made casually and are frequently influenced by chauvinism and nepotism. Too much attention is paid to race, religion, and social personality and not enough to intellect and industry. Capacity for reflection is sometimes sacrificed for aptitude at genuflection. We should reverse Caesar's axiom and regard as dangerous those men who think too little.

"The distinction between administration and leadership should be clarified in the minds of our younger faculty members. The man who concerns himself too much with administration merits comparison with Penelope—'All the yarn she spun in Ulysses' absence did but fill Ithaca full of moths.' If we can choose young men who possess both the urge to turn for themselves the pages of 'Nature's book of infinite secrecy,' and the capacity to stimulate still younger men to give their best efforts, the details of administration will—in the main—take care of themselves.

"Since, from all available indications, medical schools face a difficult period with increasing responsibilities and diminishing income, it is the duty of all faculties to search with an almost fanatical and Diogenean devotion for the best possible young men. Most of us lack the gifts of a Gilman in recognizing talent, but few mistakes will be made if we refuse to appoint an instructor, unless we are satisfied that he is a potential professor.

"Granting that the personnel of the faculty and of the student body is the most important factor in determining the strength or weakness of a medical school, there are, I believe, certain defects in our methods of instruction which could be

improved. One of these leads to a deficiency which is commonly observed in students, house officers, practitioners, and even in teachers of clinical medicine. This is an inadequate appreciation of the importance of the subjective aspects of disease. The modern medical school is often unjustly accused of an overemphasis on laboratory methods of diagnosis. The importance of these methods and of the thorough physical examination *cannot* be overemphasized. However, in our eagerness to teach these *objective* and relatively new methods of analysis, there is a tendency to forsake our heritage from Hippocrates and Sydenham and to underemphasize the older method of *subjective* analysis, i.e., the study of the patient's story of his complaints. Attending physicians, making hospital visits, are too ready to accept the history as obtained by a student, who has been inadequately trained for this important task because we have not taught him properly. We teachers know—but somehow we fail to convey it to our students—that in many patients the history is the most important diagnostic procedure and that often more skill, imagination and ingenuity are required in evaluating the story than in making the physical examination, studying a blood smear or interpreting a roentgenogram. Consider for a moment the middle-aged male who complains of recurrent attacks of pain arising in the chest and radiating to the left shoulder. In such a patient the most exhaustive investigation by objective methods will often fail to make the decision—of crucial importance to the patient—as to whether coronary artery disease is the cause of the pain. The solution of the problem has to come from a careful history which will supply the correct answer in the great majority of instances. Furthermore, the story, properly interpreted, will often give an accurate clue to the other conditions, such as diaphragmatic hernia, gastric or intestinal distention, paroxysmal tachycardia, spontaneous hypoglycemia or mediastinal lymphadenitis, which are common causes of pain in this region. Most of these disorders are amenable to treatment and can be readily discovered if their presence is suspected. They are usually overlooked because the busy physician does not take the time to ask the question which would yield the clue.

"Medicine is still an art. Not yet—and probably never—can all the processes of disease be put to crucial laboratory tests or detected by careful physical examination. We must still resort to the more primitive method of listening to the patient with a critical but open mind. Listening to the patient's heart and lungs is important but listening to his tongue is even more important. His symptoms must be clarified by careful questioning. All the peculiar things a patient says are not necessarily idiotic because we cannot at present explain them on a scientific basis. The physician who dismisses with a lofty and superior air a subjective complaint because he knows of no scientific reason for it is really concealing his own ignorance behind a pseudo-scientific screen. Withering did not do this when his patient with dropsy improved after foxglove was prescribed by the witch; Hess was humble enough to investigate the codliver oil "myth." The unraveling of the many puzzling and seemingly capricious subjective manifestations of disease will come not by dismissing them but by investigating them. A pain in the abdomen is no less a phenomenon in nature than a mass in the abdomen and both manifestations merit the physician's most careful study, even though the exploration of the former usually requires more time and a more delicate instrument—the physician's cerebral cortex rather than his knife—and is likely to be less remunerative. In this day of much needed emphasis on the importance of the objective laboratory methods of examination, we should never forget that the most valuable of all special medical tools is the fountain pen, guided by intelligence and propelled with thoroughness.

"In times past medical students often regarded their preclinical years as sojourns in a purgatory which must be endured before entering the clinical paradise. This tendency still exists to some extent and we teachers are partly at fault. We allow the division to be too sharp. I believe that during the preclinical years the students should spend one hour a day seeing patients and that during the clinical years one hour daily should be devoted to the basic medical sciences. The task of learning the sensory paths in the spinal cord would become

easier if stimulated by the sight of a tabetic gait. What student of neuro-anatomy would fail to be thrilled by an inspection of the pyramidal tract immediately after seeing for the first time an instance of hemiplegia? It is a rare professor of medicine who can compete with his colleague in biochemistry in conducting a clinic dealing with tetany or diabetic acidosis. Since our students aim at becoming physicians rather than veterinarians, is it to be wondered at that they are more interested in Starling's law of the heart when illustrated by the patient with congestive failure rather than when demonstrated by the heart-lung preparation of a dog? Is the pure science of the preclinical years so pure that it needs must be protected from clinicians by a chastity girdle of aloofness? Are the Jerichoan walls of formality which surround our wards to be so strong that the preclinical teacher or student desiring to overcome them must borrow Joshua's trumpet? A slight change in curriculum and a large change in mental attitude toward these matters would result immediately in better teaching and indirectly—because of the inevitable exchange of ideas, in improved research both for our clinical and preclinical members. Such an arrangement would increase the student's interest throughout his medical course and need not alter the total teaching hours of any department.

"During his clinical years the student of medicine has many duties but few responsibilities in regard to patients. When he becomes a house officer he is suddenly put in a position of considerable responsibility and because of it he works more diligently and learns more rapidly. I believe that undergraduates would be immensely benefited by acting as junior internes throughout their third and fourth years. Teaching hospitals should be equipped with dormitories. The cost of constructing such buildings could probably be amortized by fees paid by the students for board and room. Each undergraduate would have responsibility for a certain number of patients and his work would be supervised by a resident staff as at present. Such a plan, which is no more radical than was the now universal system of clinical clerkships when first introduced, could render the transition from student to house officer less

abrupt than at present. At the time of graduation the student would already have had something corresponding to a rotating junior interneship."

The foregoing brief evaluation of medical training in the United States in the period immediately before the present war may perhaps be summarized as follows: The undergraduate teaching needed improvement but was good in many institutions and fair in most of the others; the interneship was excellent in a few hospitals but on the whole only fair; the opportunities for advanced training as residents were—as a rule—seriously inadequate. If this was the situation in 1940, we immediately realize how much more important the defects will be at the end of the war. Whether we shall have at that time too few or too many doctors is still being debated but there is no doubt that we shall have too many poor doctors and too few good ones. The civilian physicians—harried as they are by caring for too many patients—are not keeping abreast of the advances in medical knowledge, while many of the physicians in the armed forces—inadequately taught from the beginning because of the necessity for haste—will need and wish advanced training. It is clear therefore that the great problem which confronts those institutions devoted to medical education—and this includes, of course, all of the better hospitals as well as the medical schools—is the development of an adequate program of postgraduate instruction. Unless we are able to do this we shall fail in our trust and the quality of a great profession will deteriorate.

Having defined the major problem which is approaching us—that of providing facilities for training the young physicians who return from the armed forces and desire to be better doctors, it may be permissible for us to turn our concluding thoughts toward a happier topic and to consider some of the rewards which the medical Minerva—that jealous goddess—offers to her faithful worshippers.

The physician occupies a special position in society in that he is the only person who combines training in the scientific method with occasion for contact with large numbers of the general public. Thus, opportunity places an obligation upon

him to try to set an example in objective thinking. He therefore should attempt to approach those problems—whether political, governmental or economic—which involve society as a whole with that unprejudiced scientific attitude which he utilizes in approaching the problems of the individual patient. In a world when the answers to many of the important questions confronting human society are being sought on an emotional rather than on a rational basis, the physician can render a great service if he will himself learn—and thereby teach others—that objective thought must supplant subjective feeling if the problems confronting mankind are to be wisely solved.

"Perhaps the greatest charm of medicine as a profession is the variety of facilities for happy work which it offers to men of the most diverse talents and interests. One man prefers the laboratory, another the library, a third the operating table and still another the consulting room. For the large majority of us, who are primarily interested in the sick patient, an exclusive devotion to books and laboratories leads to discontent and to Faust's complaint:

> 'I've studied now philosophy
> And jurisprudence, medicine,—
> And even alas! theology,—
> From end to end, with labor keen;
> And here, poor fool! with all my lore
> I stand, no wiser than before.'

"The opposite extreme—becoming so interested in patients that reading and laboratory work are neglected—is a disastrous error and rapidly leads first to stagnation and then to retrogression. In my opinion the greatest satisfaction comes from a judicious blending of the various types of work. A patient is seen presenting an interesting and puzzling phenomenon. A few hours in the library tells you the condition has been observed before but has never been satisfactorily explained. Various studies on the patient, conducted by the methods of the laboratory, furnish a suggestive but not a conclusive answer. It becomes necessary to make an extensive series of

investigations on animals. Finally, after a period of several years, during which the techniques of physiology, pathology, and biochemistry have been borrowed, the proof is at hand and a scientific concept has been created. Perhaps it seems unimportant even though true. Well, the thermo-dynamic concepts of Williard Gibbs seemed unimportant when he first announced them and for a long time thereafter. And in any case you did work out the concept for yourself and to do this is more satisfying than to 'cook the scraps of other's fare.' I know of no other profession which offers both the pleasure which comes from dealing with human beings and the contentment derived from exploring 'the rivers of existence.' If therefore you desire the greatest happiness in medicine, accept it as an intellectual adventure—occasionally thrilling, sometimes disappointing, usually arduous, but always interesting."

THE PHYSIOLOGICAL SIGNIFICANCE OF THE RENAL PRESSOR MECHANISM*

ERIC OGDEN

Ever since Richard Bright's brilliant description, the association between renal disease and the cardiovascular disorders now known as hypertensive has challenged investigation. After a survey of recent writings one may be pardoned for doubting whether this investigation has arrived any nearer to its early goal of finding the cause of hypertension in man.

One of the best chapters in this story is that of the discovery by Goldblatt of experimental renal hypertension which he described with rare modesty and wisdom as a method for producing chronic hypertension in laboratory animals which may be used in the study of "the pathogenesis of hypertension that is associated with renal vascular disease." His report was greeted with enthusiasm by those who thought that the Goldblatt phenomenon must be the etiological factor of much human hypertension. The course of the large amount of useful and productive work done in Indianapolis, Cleveland, Buenos Aires, London and elsewhere in studying this possibility is already too well known and too well reviewed (Braun-Menendez) to need discussion here. So also is its failure to elucidate the etiology or to provide a sound treatment for essential hypertension. (Gregory 1943, Reed 1944.)

As a tool for the study of the disturbed function and structure resulting from the hypertensive state, Goldblatt's work has already been useful and may be expected to prove increasingly valuable: *as a physiological phenomenon it is challenging to an extreme degree.* The concluding paragraph of Barcroft's *Architecture of Physiological Function* sounds this challenge inimitably, "Accidents happen in nature as elsewhere, but—I range myself on the side of those that regard a phenomenon as more likely to have a significance than not. Those who think with me must shoulder the burden of dis-

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covering what the significance may be, but on our opponents rests the much heavier burden of proving the phenomenon to be an accident, if indeed it be such."

What is the significance of the Goldblatt phenomenon? Teleologically speaking, why should there be a mechanism for producing hypertension and all its attendant evils? How could such a mechanism evolve?

The ground plan of the answer to these questions has already been sketched by Sapirstein, Southard and Ogden, Collins and Hamilton, and Huidobro and Braun-Menendez. Independently and simultaneously these three groups began to work on the possibility that the Goldblatt phenomenon might be evoked by other means more likely to occur commonly in nature than constriction of the renal arteries. A brief review of the considerations which led to this work will help us to orient its significance.

In 1940 Kohlstaedt and Page found that renin, the first known component of the renal pressor system, is liberated by a perfused kidney when the pulse-pressure of perfusion is reduced. The intricacies of the technique, the uncertainty of the assay methods used at that time, and skepticism as to the value of a perfused kidney diverted attention from the great importance the observation would have if substantiated. About the same time, Page observed experimental hypertension, generally accepted as being of the Goldblatt type, occurring when a hard perinephritic inflammatory capsule was induced. In terms of the original experiments of Goldblatt here was a new way of producing "ischemia" by a constricting capsule obstructing the blood flow to the kidney. A little later, Corcoran and Page showed that experimental renal hypertension could be brought about by a renal artery "constriction" insufficient to cause any diminution in blood flow. Yet the word "ischemia" in this connection dies slowly!

A suggestion which has not had all the consideration it seems to deserve is that the precipitating cause of renin liberation and thus of renal hypertension may be the failure of expansile pulsation of the kidney. It may be that the motionless kidney liberates renin whether it is motionless from renal

artery constriction, from diminished aortic pulse-pressure, or from the splinting effect of cellophane perinephritis. A careful consideration of recent observations as well as a critical review of the earlier literature makes it seem increasingly evident that ischemia plays little if any part in renal hypertension and that, in many instances at least, diminished pulse-pressure or renal immobility is paramount.

While the pulse-pressure idea was still new and reasonably controversial, Sapirstein decided to study this question in the whole animal since the excised kidney had been criticised as being too abnormal as a basis for an important conclusion. He was at that time engaged in evaluating the very unsatisfactory techniques then available for examining blood for renin, hypertensinogen, and hypertensin. A chance error resulted in the observation that a postoperative patient had blood strikingly dissimilar from that of a preoperative patient in the same ward. The dissimilarity was manifest in its effect on smooth muscle, but the phenomenon has not yet been adequately studied in man. This called his attention to the well known fact that trauma, hemorrhage, and surgery produce varying degrees of shock characterized by accelerated pulse rate and diminished pulse pressure.

Sapirstein immediately studied the gut-stimulating properties of blood before and after severe hemorrhage and correctly inferred that severe hemorrhage resulted in an increased secretion of renin (referable to the diminished pulse-pressure), and increased production of hypertensin, and a diminution in the hypertensinogen content of the blood.

Perhaps somewhat similar mental processes were active at the same time in Philadelphia and Buenos Aires, for this inference was immediately supported and amplified by the more extensive work of Collins and Hamilton which was already in the press and that of Huidobro and Braun-Menendez which was ready for printing at the time Sapirstein's work appeared. It seems odd that although these three schools have been engaged in this work at least since 1941 there has been no real discussion to date of the fundamental importance of this demonstration that the mechanism unearthed in Gold-

blatt's search for hypertension is in fact *part of a normal regulatory mechanism.* The three groups referred to, and also Doctor Lewis Dexter who continued his work in this field after leaving Buenos Aires—have each continued to bear their share in the development of our present understanding of the subject.

The demonstration by Ogden, Page, and Hildebrand that an animal might be tachyphylactic to its own renin was quickly followed by Sapirstein, Southard, and Ogden, who showed that fatal hemorrhage could be temporarily averted by blood globulin concentrates in small quantities. These concentrates were demonstrably rich in hypertensinogen, but if they were denatured, or if similar quantities of gelatin were used, no effect was observed. For these reasons it was felt that the action is not due to the colloidal osmotic pressure but is evidence of exhaustion and replacement of hypertensinogen and it was felt that hypertensinogen exhaustion might well be an important factor in fatal hemorrhagic shock.

Braun-Menendez contributed, among many other valuable observations, the very significant fact that hypotension induced by intravenous barbiturates could produce renin liberation within a few minutes.

Hamilton and Collins published very carefully controlled work which did perhaps more than that of the other groups to give an acceptable degree of certainty to the concept that hemorrhage and shock would cause renin liberation. But in many ways one of their most significant experiments was that in which an animal liberated measurable renin in response to a hemorrhage so small that it did not affect the blood pressure. May we assume that it accelerated the pulse and thus reduced the pulse pressure?

The established facts then are that disturbances of vascular dynamics (Sapirstein, Southard, and Ogden) even though very slight (Hamilton and Collins) may produce almost immediately (Huidobro and Braun-Menendez) a compensatory release of renin. This by its action on arterial muscle tends to raise the mean arterial pressure and thus perhaps reflexly by slowing the heart via the depressor nerve tends to increase

the pulse pressure. This is the essence of a homeostatic endocrine action.

That this system breaks down by exhaustion when stimulated too violently and produces disease when stimulated too chronically by a Goldblatt clamp is a pathological accident which has led us to appreciate the true significance of the Goldblatt phenomenon—*that the renal pressor system must take its stand along with the adrenal medulla and the posterior lobe of the pituitary body as one of the fundamental endocrine homeostatic systems which serve for the regulation of the circulation for the needs of the body as a whole* and are superimposed upon the local metabolic "self-government" of the vascular system as it serves individual regions and organs. This endocrine circulatory control in turn is subordinate to the more labile but much better understood reflex system which serves two functions, first to protect the brain's blood supply and that of the heart, second to initiate rapid adaptations to fear, pain, exercise, and other emergency. A failure to recognize this hypotactic subordination of the three cardiovascular control systems and to appreciate the relative stability of the chemical as contrasted with the lability and imperfections of the nervous mechanisms may have led to a good deal of the confusion that exists in the understanding and recognition of functional disorders of the cardiovascular system and of cardiovascular manifestations of nervous disease.

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CALLING ATTENTION TO:

Items of Possible Interest to Our Friends

1. Streamlined Medical Journals: Here's to R. C. Ransdell's snappy *U. S. Naval Medical Bulletin*, in the February issue of which E. Holman's "Working Rules in the Field" ring the bell for helpful medical advice (42:275). Helpful also is G. W. Calver's bibliography on shock (*Ibid.*, pp. 365–380). Always business-like with no space wasted is *Psysiological Reviews*, January issue contains E. E. Osgood's "Cellular Composition of Bone-Marrow" (24:46); W. W. Swingle's "Role of the Adrenal Cortex" (p. 89); E. W. McHenry's "Lipotropic Factors" (referring to chlorine, lipocaic, and inositol, p. 128), and L. H. Newburgh and J. W. Conn's discussion of "Obesity" (p. 18). Even *The Scientific Monthly* has been snapped up!

2. Antibiotics: E. McCawley says E. J. Poth and C. A. Ross's phthalylsulfathiazole (*Texas Rep. Biol. Med.*, 1:345, 1943) marks the end of an era: now for antibiotics! Pioneering S. A. Waksman & Co. describe "Streptomycin" from Streptomyces as effective vs. Gram positive and negative bacteria (*Proc. Soc. Exp. Biol. Med.*, 55:66, 1944). P. Gyorgy and P. C. Elmes (*Ibid.*, p. 76) find non-deliquescent calcium salt of penicillin no more toxic for man than Na-salt, contrary to Florey's advice (*Lancet*, 1:387, 1943). N. Atkinson and N. Stanley find that SH cmpds such as thioglycollates, glutathione and cysteine specifically suppress "penicidin" either by reduction or enzyme competition (*Australia J. Exp. Biol. Med.*, 21:249, Dec., 1943). J. W. Foster and H. B. Woodruff show that dissociated streptothricin loses activity (*Arch. Biochem.*, 3:241, Dec., 1943). Patulin, from Penicillium patulin (H. Raistrick, *Lancet*, 245:633, 1943), found identical with S. Waksman's "clavacin" from Aspergillus clavatus (I. Hooper, *Science*, 99:16, 1944), is now reported identical with "claviformin" from Penicillium claviforme (E. Chain & Co., *Lancet*, 246:112, Jan. 22, 1944). How about penicillin? When do we get over the hush-hush and argument about its composition?

3. Chemotherapy: O—O! P. C. Sen Gupta notes neuropathic sequelae after diamidinostilbene therapy in kala-azar (*Ind. Med. Gaz.*, 78:537, Nov., 1943). J. V. Scudi and V. C. Jelenek report urinary excretion of atabrine complex, with some atabrine appearing unchanged (*J. Biol. Chem.*, 152:27, 1944). H. G. Barbour & Co. show B-tetrahydronaphthylamine aids in recovery in hypothermia and hydration from chilling (*Yale J. Biol. Med.*, 16:231, 1944). R. L. Cahen & Co. report morphine not specific in depressing cortical electrical activity, but that morphine reduces tissue permeability (*Ibid.*, p. 239, 257). Trust the English to beat the silly censor: H. E. Holling & Co. discuss prevention of sea sickness by drugs, finding hyoscine in doses around 1 mgm most useful (*Lancet*, 246:127, Jan. 22, 1944). Maybe R. T. Fick & Co.'s report will quiet the too long foolishness of ethylene disulfonate in a dilution of $1:10^{-15}$ for asthma! (*J. Allergy*, 15:14, 1944).

4. ETC.: E. Gutmann and J. Z. Young make important study on reinervation of muscle after various periods of atrophy (*J. Anat.*, 78:15, 1944). W. P. Chapman and C. M. Jones begin careful study on variations in pain-perceptions and pain-reactions in average humans (*J. Clin. Invest.*, 23:81, 1944). T. S. Danowski suggests use of thiourea as a measure of change in body water (*J. Biol. Chem.*, 152:207, 1944). G. H. Bourne shows ascorbic acid necessary for usual phosphatase activity and bone deposition (*J. Physiol.*, 102:319, Dec. 31, 1943). M. Vogt in studying cortical hormone output finds rapid inactivation (*Ibid.*, p. 356). P. E. Steiner & Co. report a toxic factor in tissues of cases of nonspecific ulcerative colitis (*Proc. Soc. Exp. Biol. Med.*, 55:8, 1944). G. Decherd, A. Ruskin and G. Herrmann describe momentary atrial electrical axes in paroxysmal tachycardia (*Ibid.*, p. 17). A. J. Salle and H. L. Guest find increased efficiency of phenolic germicides on adding ferrous and ferric salts to produce redox systems (*Ibid.*, p. 26). M. G. Goldner and G. Gomori say that alloxan causes diabetes by direct injury to beta cells (*Ibid.*, p. 73). W. Modell and S. Krop find that in terms of effective mercury, non-ionizable organic mercurials are not less toxic than mercury bichloride (*Ibid.*, p. 80). And H. S. Burr discusses the effect of the moon on tree growth (*Yale J. Biol. Med.*, 16:249, 1944).

5. PRESSES STILL ROLL: K. Stern and R. Willheim's *Biochemistry of Malignant Tumors* (Reference Press, N.Y., 1943, $12.00) is reviewed with rich wisdom by M. Shimkin (*Scien. Month.*, 58:243, 1944). Oxford Press offers L. T. More's *Life and Works of the Hon. Robert Boyle* (N.Y., 1944, $4.50—but why always the Hon.?). Oxford Press also sells M. G. Mulinos' *Pharmacology* in its outline series and it deserves expansion to a real text (N.Y., 1944, $4.50). University of California Press announces *Language and Thought in Schizophrenia*, edited by J. S. Kasanin (Berkeley, 1944, $2.00). Lippincott offers A. L. Barach's *Principles and Practice of Inhalation Therapy*, with lots of war applications (Phila., 1944, $5.00). Amer. Asso. Adv. Sci. sells symposium on *Surface Chemistry* for $3.25 (Washington, 1944). Saunders publish J. B. Erich and L. T. Austin's *Traumatic Injuries of Facial Bones* (Phila., 1944, $6.00).

6. DELAYED FROM ABROAD: S. R. Numans and E. Havinga find that local anesthetics quickly permeate epidural membranes (*Rec. Trav. chim.*, 62:497, 1943). F. Grosse-Brockhoff discuss effects of acute cooling, action of analeptics in, and recommend atropine and lactose in treatment of (*Arch. Exper. Path. Pharmakol.*, 201:417–467, 1943). R. Pulver and H. Hartin discuss biochemorphology of N_1 acyl sulfonamide derivatives (*Ibid.*, p. 491). A. Szent-Gyorgi discusses chemistry of muscle (*Bull. Soc. Chim. Biol.*, 25:242, 1943). F. K. Cramer and V. G. Foglia show experimental diabetic cataract develops proportionally to degree of hypoglycemia after pancreatectomy (*Rev. Soc. Argentina Biol.*, 19:483, 1943). L. E. Napier and P. C. S. Gupta reveal that massive non-physiological hemolysis occurs on giving hemolytic serum (*Ind. J. Med. Res.*, 31:75, 1943). A. C. Roy shows fragility of erythrocytes in hypotonic solution varies inversely

with average diameter and that surface tension plays secondary role in hemolysis with hemolytic agents (*Ibid.*, pp. 103, 109). William Evans well reviews triple heart rhythm (*Brit. Heart J.*, 5:205, 1943).

7. NEW JOURNALS: Plushily sleek, why restricted? *Air Surgeon's Bull.* appears with fancy drawings and layout: March issue containing C. E. Kossmann's article on responses of body to cold, and F. E. McDonough's management of air-sick aviator. C. C. Thomas hits *Time* with *Journal of Neurosurgery*, opening properly with G. Horrax's account of Harvey Cushing's contributions to neurosurgery, and F. D. Ingraham and O. T. Bailey's notes on fibrin foams as hemostatic agents and fibrin films in repair of dural defects without adhesions.

8. NEUROPHYSIOLOGY: A. Shapiro & Co. find plasma clot tensile strength in nerve suturing proportional to cross section of tubes in which formed (*J. Lab. Clin. Med.*, 29:282, 1944). E. J. Carey continues remarkable studies on ameboid motion and secretory activity of motor end plates, now describing drug effects (*Amer. J. Path.*, 20:341, 1944). S. W. Kuffler shows that deficient calcium first increases sensitivity of motor end plates and then blocks, while excess depresses by lowering electrical excitability of muscle fibers near end plate (*J. Neurophysiol.*, 7:17, 1944). G. H. Bishop describes peripheral unit of pain (*Ibid.*, p. 17). F. N. Craig reports important study on effect of carbon dioxide tension on metabolism of brain and medulla (*J. Gen. Physiol.*, 27:325, 1944). W. Ashby correlates carbonic anhydrase with functional levels of central nervous system (*J. Biol. Chem.*, 152:235, 1944).

9. CHEMOTHERAPY: N. M. David, N. Phatak, and F. B. Zener give much needed report on toxicity and absorption of di-iodo-hydroxyquinolin for amebiasis (*Amer. J. Trop. Med.*, 24:29, 1944). W. H. Feldman & Co. (*Am. J. Med. Sci.*, 207:290, 1944) confirm M. I. Smith et al. (*J. Pharmacol. Exp. Therap.*, 74:163, 1943) that 4,4′ diamino-diphenylsulfone successfully combats expt. TB without undue toxicity. E. F. Geever warns that skin eruptions in sulfadiazine therapy are dangerous (*Ibid.*, p. 231). E. Bigg & Co. describe use of glycol vapors for bacterial control of large spaces (*Ibid.*, p. 361). E. C. Hoff and C. Yahn find dilantin may reduce decompression convulsions (*Am. J. Physiol.*, 141:7, 1944). T. A. Loomis & Co. find sulfanilamide is excreted in humans by glomerular filtration plus tubular reabsorption (*Ibid.*, p. 158). Reviving ancient Egyptian use of garlic, leeks and onions for wounds as in Hearst Medical Papyrus prescriptions 23, 95, etc., B. Tokin, I. Toropsey & Co. review plant bactericides (*Am. Rev. Sov. Med.*, 1:251, 1944). L. P. Garrod, A. Fleming, E. Chain, M. E. Florey give best review of penicillin (*Brit. Med. Bull.*, 2:1, 1944).

10. HEALTH SERVICES: Department of Health for Scotland issues brochure on *National Health Service* (London, 1944) with emphasis on general practitioner service. In New Zealand A. Bush & Co., with D. Robb, discuss *A National Health Service* (Wellington, 1943) with emphasis on community medical centers feeding polyclinics which in turn feed hospitals. How about our individualists discussing retainer fee practice?

11. AGAIN SOME BOOKS: Grune & Stratton announce B. Dattner's *Management of Neurosyphilis*, N.Y., 1944), and also S. J. Beck's *Rorschach's Test* (2 vols., N.Y., 1944). I. A. Abt recalls his past pleasantly in *Baby Doctor* (N.Y., 1944). Columbia Univ. Press issues F. Schrader's *Mitosis*, J. K. Hall's *100 Years of American Psychiatry* and C. P. Oberndorf's intriguing *Psychiatric Novels of Oliver Wendell Holmes* (all N.Y., 1944). Putnam's publish O. Floyd's *Doctora in Mexico* (N.Y., 1944). Ronald Press issues *Personality and Behavior Disorders*, edited by J. M. Hunt (2 vols., N.Y., 1944). Asa Chandler's *Eater's Digest* rates a reprinting (Farrar, N.Y., 1944). Univ. of Texas Press issues H. Leipziger's *Architectonic City in the Americas*, containing a plea for environmental physiology and hygiene (Austin, 1944). B. Kisch monographs *Strophanthin* (N.Y., 1944). *Annual Review of Physiology* (Stanford, 1944) is usual "must" with versified preface, and new dope on neoplastic growth (J. Furth), energy metabolism (M. Kleiber), skin (S. Rothman and P. Flesch), liver and bile (L. A. Crandall), kidney (E. Braun-Menendez), vision (F. Weymouth), physiological psychology (W. Freeman and J. W. Watts) and industrial physiology (E. Simonson). *Annual Review of Biochemistry* is due in June with new material on fungi (E. Tatum) and histochemistry (D. Glick).

12. PHYSICAL THERAPY: Watch for important consequences from impending Baruch Committee Report. P. Bauwens discusses electrodiagnostic interpretations in nerve lesions (*Brit. J. Phys. Med. Indust. Hyg.*, 7:2, 1944). H. Burt offers advice on low back pain prevention and treatment (*Ibid.*, p. 7). M. E. Pusitz and I. E. Thompson describe successful physical therapy in compression fracture of spine (*Physiotherap. Rev.*, 24:51, 1944). Galveston's pre-eminence in health work explained, you noted, in its thalassotherapeutic advantages (C. I. Singer and K. Phillips, *J. A. M. A.*, 124: 1128, April 15, 1944).

13. CHEMOTHERAPY: G. J. Martin reviews acridine antiseptics (*Medicine*, 23:79, 1944). E. M. Osborn finds antibiotics in fresh green Ranunculaceae, especially Anemone apennina, Clematia recta and Helleborus viridis (*Brit. J. Exp. Path.*, 24:227, Dec., 1943). Excellent review with bibliography of penicillin by E. Chain and H. W. Florey (*Endeavor*, 3: No. 9, 3, 1944). J. T. Culbertson and H. M. Rose find stibamine glucoside useful in experimental rat filariasis (*Science*, 99:245, March 24, 1944). O. L. Peterson finds toluidine blue effective against mice typhus (*Proc. Soc. Exp. Biol. Med.*, 55:155, 1944). W. B. Dunham & Co. show *in vitro* action of penicillin vs. Treponema pallidum and that inadequate therapy produces resistant strains (*Ibid.*, p. 158).

14. ETC.: Lots of fine neurophysiology in Fasc. 4, vol. 1, *Helvetica Physiol., Pharmacol. Acta*, especially M. Monnier on brain-stem topography, S. Burgi on Substantia reticularis, and W. R. Hess on co-ordination. B. H. Robbins succeeds is producing experimental cataract with dinitrophenol (*J. Pharmacol.*, 80:204, 1944). R. A. Izzo and A. D. Marenzi show relation of kidneys and protein to blood lipids (*Rev. Soc. Argentina Biol.*, 19:547, 576, Dec., 1943). C. P. Leblond shows thiourea increases resistance

to anoxia by depression of thyroid (*Proc. Soc. Exp. Biol. Med.*, 55:114, 1944). How about giving to fliers? W. B. Beveridge and F. M. Burnet describe cutaneous reaction to influenza virus (*Med. J. Australia*, 31:85, Jan. 29, 1944). M. H. Sloan and E. Shorr indicate physiology of remission in Graves disease caused by thiouracil (*Science*, 99:305, April 14, 1944). S. F. Cook describes conflict between California Indian and white civilization (*Univ. Calif. Publ. Ibero-Americana*, No. 21–24, 1944). W. MacNider shows structural stabilization with aging in adaptation to injury (*Proc. Soc. Exp. Biol. Med.*, 55:226, 1944). E. A. Brown offers index of commercial mixtures for asthma (*Ann. Allergy*, 2:29, 1944). F. R. Edwards notes successful despeciated bovine serum substitute for human plasma (*Brit. Med. J.*, 1:72, Jan. 15, 1944). January, 1944 issue *Journ. Mental Science* is special number surveying recent progress in psychiatry.

15. OLEANDERS (GALVESTON ORCHIDS) To: F. H. Redewill, A. L. Rose, and Mead Johnson & Co. for arranging the 7th annual exhibition of the American Physicians Art Asso. at the Stevens Hotel, Chicago, for the A.M.A. meeting June 12–16; the A.M.A. section officers for a swell program (*J.A.M.A.*, 125:40–70, May 6, 1944); E. P. Mumford and J. L. Mohr of Stanford for their forthcoming free *Manual on Distribution of Communicable Diseases and Their Carriers in the Pacific Islands;* I. Chavez on his fine Instituto Nacional de Cardiologia in Mexico City, with the great Diega Rivera frescos on the history of cardiology, and to R. Pratt, T. C. Daniels, J. J. Eiler, J. B. Gunnison, W. D. Kumler, J. F. Oneto, L. A. Strait, H. A. Spoehr & Co. for finding antibiotic "chlorellin" in chlorella algae which can be so easily grown (*Science*, 99:351, April 28, 1944). Also to J. Mitchell for a worthy essay on rats and plague in the April 28th *New Yorker*. And to Alien Property Custodian for issuing first list of available foreign titles from Edwards Bros., lithoprinters at Ann Arbor.

16. CANCER: Should be "cancers,"—M. Shimkin says we should differentiate cancers and not speak of "cancer" as a single disease. L. Gross raises question of cancers being biologically communicable, but omits reference to J. Beard's collected papers issued by Chatto & Windus in London in 1911 (*Cancer Res.*, 4:293, 1944). D. Burk & Co. continue studies on production of malignancy *in vitro*, and discuss blood proteose in cancers, (*J. Nat. Cancer Inst.*, 4:363, 417, 1944).

17. CHEMOTHERAPY: A. Albert reviews cationic chemotherapy with reference to acridines (*Med. J. Australia*, 1:245, March 18, 1944). Resistance of organisms to sulfonamides is surveyed by W. T. Goodale and L. Schwab, and also by W. W. Spink and J. J. Vivino (*J. Clin. Invest.*, 23:217, 267, 1944). Winthrop issues second series of its annotated bibliography on penicillin.

18. FEDERATED PROCEEDINGS: K. H. Beyer and A. R. Latven say succinate shortens barbital narcosis (*Fed. Proc.*, 3:4, 1944). A. H. Brown and R. E. Gosselin confirm reduction of water loss by shade and clothes wetting (*Ibid.*, 5). V. Johnson & Co. show that high fat diet taxes bone marrow in recovery from hemorrhagic anemia (p. 8). A. Grollman finds

that oxidized marine oils lower experimental hypertension (p. 15). J. T. Hart and W. A. Selle find that urea peroxide contracts smooth muscle (p. 17). H. A. Haterius and E. Glassco confirm M. Prinzmetal that liver extract protects against fatal burn shock. A. M. Hughs notes that thiouracil protects against high altitude anoxia and CO poisoning, but not against cyanide (p. 21). M. B. Visscher & Co. report that high oxygen intake increases metabolism and reduces shivering (p. 26). S. O. Levinson & Co. propose standardized method to produce shock for plasma substitute assay (p. 29). N. S. Maluf says negative intrapleural pressure is result of retractile tension of lungs (p. 31). E. Ogden and C. F. Dalziel analyse sensations during passage of constant galvanic current (p. 35). R. K. Richards and G. M. Everett describe analygesic and anticonvulsant action of 3,5,5-trimethyloxalidine 12,4-dione, tridione (p. 39). G. E. Wakerlin & Co. confirm value of renal extracts in treating spontaneous hypertension (in dogs) (p. 50). The Fraenkel-Conrats discuss pituitary control of blood insulin level (p. 57). H. H. Anderson and H. Y. Soong are pessimistic on chemotherapy of experimental leishmaniasis (p. 64). J. H. Draize describes methods for studying skin absorption (p. 69). J. K. Finnegan notes anticonvulsant action of diethylsuccinyl urea (p. 72). C. A. Handley & Co. find amphetamine best antagonist to morphine (p. 75). J. L. Morrison notes choleretic action of halogenated fatty acids (p. 83). A. A. Nelson notes hepatic injury from atabrine (p. 91).

19. ETC.: D. Marsh's notes on management of civilian war gas injury appear (*Ann. Int. Med.*, 20:376, 1944). H. S. Mayerson discusses physiology of orthostatic circulatory failure (*Amer. J. Physiol.*, 141:227, 1944), now treated clinically by R. Gregory with desoxycorticosterone and sodium chloride. A. Hemmingway analyses cold sweating in motion sickness (*Ibid.*, p. 172); C. Entenman & Co. note effectiveness of lipocaic in preventing fatty livers (*Ibid.*, p. 221). H. S. Bennett & Co. describe effect of anesthetics on normal and shock circulation (*J. Clin. Invest.*, 23:181, 1944).

20. IT IS SAID: By Arno Luckhardt that Univ. Chicago Press's symposium on *Medicine and the War* is excellent. It is. That R. West's *Conscience and Society: A Study of the Psychological Prerequisites of Law and Order* (Methuen, London, 1943) is worth reading. It is. That K. J. W. Craik's *The Nature of Explanation* (Cambridge Univ. Press, 1943) is worth study. It is. That *Advances in Enzymology*, Vol. 4 (edited by F. F. Nord and C. H. Workman, Interscience Publishers, N.Y., 1944) is worth ordering. It is. That M. B. Jacobs well edited *The Chemistry and Technology of Food and Food Products* (2 vols. at $19.00, Interscience Publishers, N.Y., 1944). He did. That Otto Glasser deserves much congratulation, with his collaborators, for compiling the encyclopedic *Medical Physics* (1 vol. at $19.00, Year Book Publishers, Chicago, 1944). He does.

21. HAVE YOU SEEN: Sir Thomas Lewis's reflections on reform in medical education (*Lancet*, May 13, 20 and 27, 1944)? H. E. Sigerist's comments on the University at the cross-roads (*Bull. Hist. Med.*, 15:233, 1944)? Alan Gregg's question, "Can excellence be learned? (*Journ. Asso.*

Amer. Med. Coll., 19:105, 1944)? The provocative report of the Baruch Committee on Physical Medicine (597 Madison Ave., N.Y., 1944)? M. Neuburger's survey of the concept of nature from a medical standpoint (*Isis*, 99:16, 1944)? C. J. Herrick's discussion of the incentives of science (*Sci. Month.*, 58:462, 1944)? And Alan Gregg's further philosophical critique of medical research (*Sci. Month.*, 58:365, 1944)? If not—better take a look.

22. Control of Air-borne Bacteria: Conclusive evidence comes from A. P. Krueger and Co. (*Naval Med. Bull.*, 42:1288, 1944) that glycol sprays are not as effective as proper floor oiling in controlling droplet-dust infection spread in hospitals or public places. Wholly independent confirmation comes from three British groups, J. Wright & Co., F. C. Harwood & Co., and P. H. R. Anderson & Co. (*Brit. Med. J.*, 1:611, 615, and 616, May 6, 1944) that oiling floors and bed clothes controls dust-borne infections in hospitals and public places. No wonder K. F. Meyer jumped us for recommending glycols!

23. British Medical Bulletin: Published by British Council, Medical Dept., 3 Hanover St., London, W1, goes to town again with special number on drugs (Vol. 2, 1944). F. H. K. Green discusses clinical evaluation of new remedies (p. 58). W. Yorke reports on aromatic diamidines in protozoal infections (p. 60). F. Hawking summarizes recent work on the pharmacology of sulphonamides (p. 70), and surveys biological standardization of neoarsphenamine (p. 70). The Faraday Society symposium on modes of drug action is fully abstracted, as are antimalarials, new synthetics and local reactions in routes of administration.

24. Of interest: J. F. Rinehart's cautious note on treating rheumatic fever with crude hesperidin (vitamin P) may be something (*California's Health*, 1:22, May 31, 1944). I. I. Kaplan's cautious note on treating cancer with avidin (egg white) also may be something (*Amer. J. Med. Sci.*, 207:733, 1944). R. B. Roth notes surprising incidence of trichomonad infection of male genital tract (*VD Info.*, 25:163, 1944). J. S. K. Boyd and B. Portnoy show conclusively that bacteriophage has no action *in vivo* comparable to what it has *in vitro* in bacillary dysentery (*Trans. Roy Soc. Trop. Med. Hyg.*, 37:243, 1944). J. C. Aub reviews physiologic aspects of traumatic shock (*J. Indust. Hyg. Tox.*, 26:183, 1944). W. and G. Henle find that influenza virus inactivated by ultra-violet or 56° C. interferes with growth of active influenza virus (*Amer. J. Med. Sci.*, 207:705, 717, 1944). S. Sunderland calls attention to deceptive muscle action in peripheral nerve lesions (*Austral. N. Zea. J. Surg.*, 13:160, 1944). W. D. Paul and C. R. Kemp show that methemoglobin averages 0.1 per cent in normal humans (*Proc. Soc. Exp. Biol. Med.*, 56:55, 1944).